Computational Anatomy Using Deformation Morphometry

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Challenge

- Clinical studies aim to describe effect of disease/treatment on brain
- Where to look for effects?
- Anatomic variability
- Manual methods: time consuming, rater error
- Goal: automatically measure differences, look everywhere, account for anatomic variability, high power

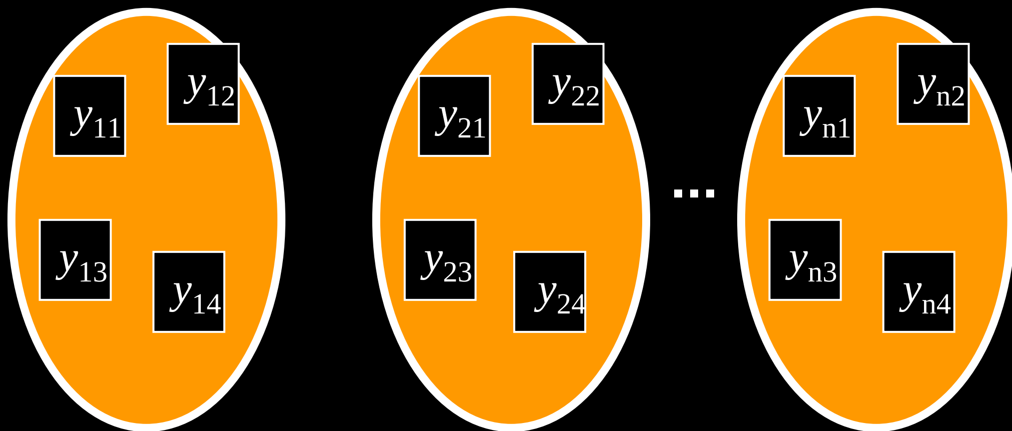
Voxel-Based/Deformation Morphometry

- Automated
- Suited for discerning patterns of structural change
- Explore location and extent of variation
- Use nonlinear registration or “warping” of images
  - Within: capture changes in brain over time
  - Between: measure deviation from atlas brain
  - relate anatomy to clinical/functional variables
- Low power

Statistical Model

- Multivariate general linear model
- Dependent variable is tissue density (VBM) or property of the transformation between images (DBM)
- Model effects of interest
  - Continuous variable (e.g. MMSE)
  - Group variable (e.g. treatment)
- Model confounding variables (e.g. age, sex)
- Create and interpret statistical map
  - statistic evaluated at each voxel
  - voxels where statistic exceeds threshold show regions of significant differences

$$voxvol = diag \cdot \beta_1 + age \cdot \beta_2 + score \cdot \beta_3$$



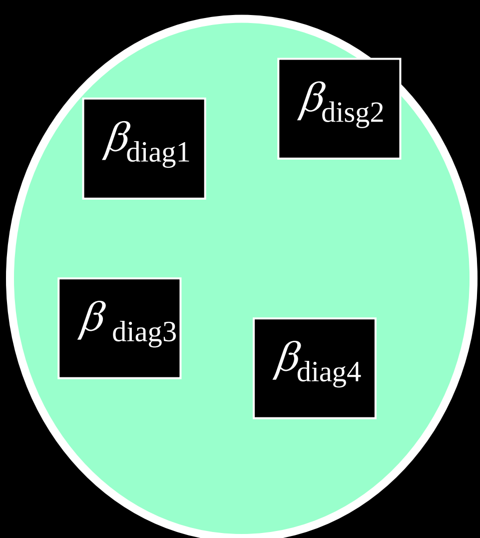
Map 1;
diagnosis 0
age 65
score 16

Map 2;
diagnosis 1
age 68
score 8

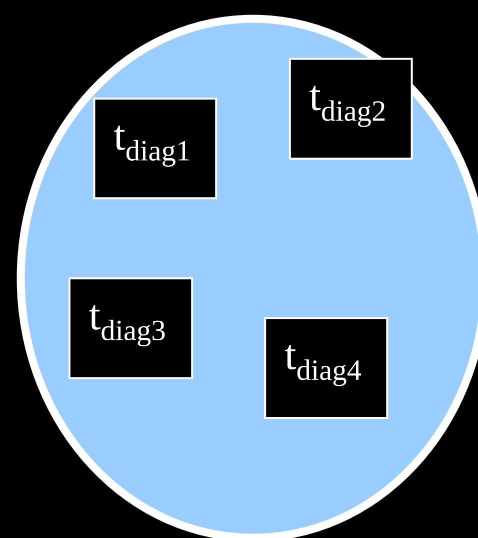
Map n;
diagnosis 1
age 73
score 4

$$\begin{bmatrix} y_{11} \\ y_{21} \\ \vdots \\ y_{n1} \end{bmatrix} = \begin{bmatrix} 0 & 65 & 16 & 1 \\ 1 & 68 & 8 & 1 \\ & & \ddots & \\ 1 & 73 & 4 & 1 \end{bmatrix} \begin{bmatrix} \beta_{diag1} \\ \beta_{age1} \\ \beta_{score1} \\ \beta_{\mathrm{int}1} \end{bmatrix}$$

$$\begin{bmatrix} y_{12} \\ y_{22} \\ \vdots \\ y_{n2} \end{bmatrix} = \begin{bmatrix} 0 & 65 & 16 & 1 \\ 1 & 68 & 8 & 1 \\ & & \ddots & \\ 1 & 73 & 4 & 1 \end{bmatrix} \begin{bmatrix} \beta_{diag2} \\ \beta_{age2} \\ \beta_{score2} \\ \beta_{\mathrm{int}2} \end{bmatrix}$$



coefficient maps for each variable



statistic maps for each variable

Ordinary Least Squares

$$\mathbf{y}(v_i) = \mathbf{A}\beta(v_i) + \mathbf{e}, \qquad \min_{\beta} \mathbf{e}^T\mathbf{e} = \min_{\beta} \left\| \mathbf{y}(v_i) - \mathbf{A}\beta(v_i) \right\|^2$$

$$\beta(v_i) = (\mathbf{A}^T\mathbf{A})^{-1}\mathbf{A}^T\mathbf{y}(v_i)$$

- y: $n \times 1$ observations, subjects
- A: $n \times p$ independent variables
- β: $p \times 1$ regression coefficients
- **e**: $n \times 1$ residuals
- Solution valid if A^TA full-rank

Computation

- Compute $(A^TA)^{-1}A^T$, solve for estimates β at each voxel
- More efficient to use matrix decomposition
  - Cholesky decomposition: $A^TA=LL^T$
    - $Lb(v_i)=A^Ty(v_i)$
    - $b(v_i)=L^T\beta(v_i)$
    - L lower triangular so easy to solve
  - L is computed from left to right and top to bottom!

The Multiplicity Problem

- Map formed of ~2 million correlated statistics
- Bonferroni procedures too stringent
- Measurements of volume change are not independent, due to
  - initial image resolution
  - spatial transformation
  - smoothing

Corrections for Multiple Comparisons

- Permutation testing
  - Build a null distribution
  - Compare statistic from experiment to assess significance
- Cluster analysis
  - Only consider voxels above predetermined threshold
  - Create clusters of neighboring voxels
  - Cluster exceeding a certain size are significant

Nonparametric Permutation Testing

- Observations are labeled (e.g., AD, control, sex)
- Compute a statistic expressing the experimental effect (e.g., t-statistic comparing AD vs. control)
- Permute labels, re-compute statistic, repeat in order to build a distribution
- Compare statistic computed from original labels to distribution to assess significance

Example

Original labels
t=6

$$\begin{bmatrix} y_{11} \\ y_{21} \\ \vdots \\ y_{n1} \end{bmatrix} = \begin{bmatrix} 0 & 65 & 16 & 1 \\ 1 & 68 & 8 & 1 \\ & & \ddots & \\ 1 & 73 & 4 & 1 \end{bmatrix} \begin{bmatrix} \beta_{diag1} \\ \beta_{age1} \\ \beta_{score1} \\ \beta_{\text{int}1} \end{bmatrix}$$

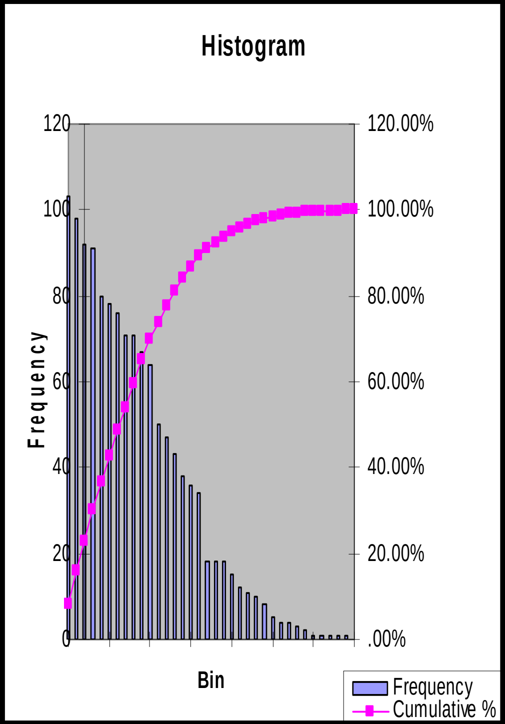
Permutation 1
t=0.5

$$\begin{bmatrix} y_{11} \\ y_{21} \\ \vdots \\ y_{n1} \end{bmatrix} = \begin{bmatrix} 0 & 65 & 16 & 1 \\ 1 & 73 & 4 & 1 \\ & & \ddots & \\ 1 & 68 & 8 & 1 \end{bmatrix} \begin{bmatrix} \beta_{diag1} \\ \beta_{age1} \\ \beta_{score1} \\ \beta_{\text{int}1} \end{bmatrix}$$

repeat 1000 times

Permutation 1000
t=1.5

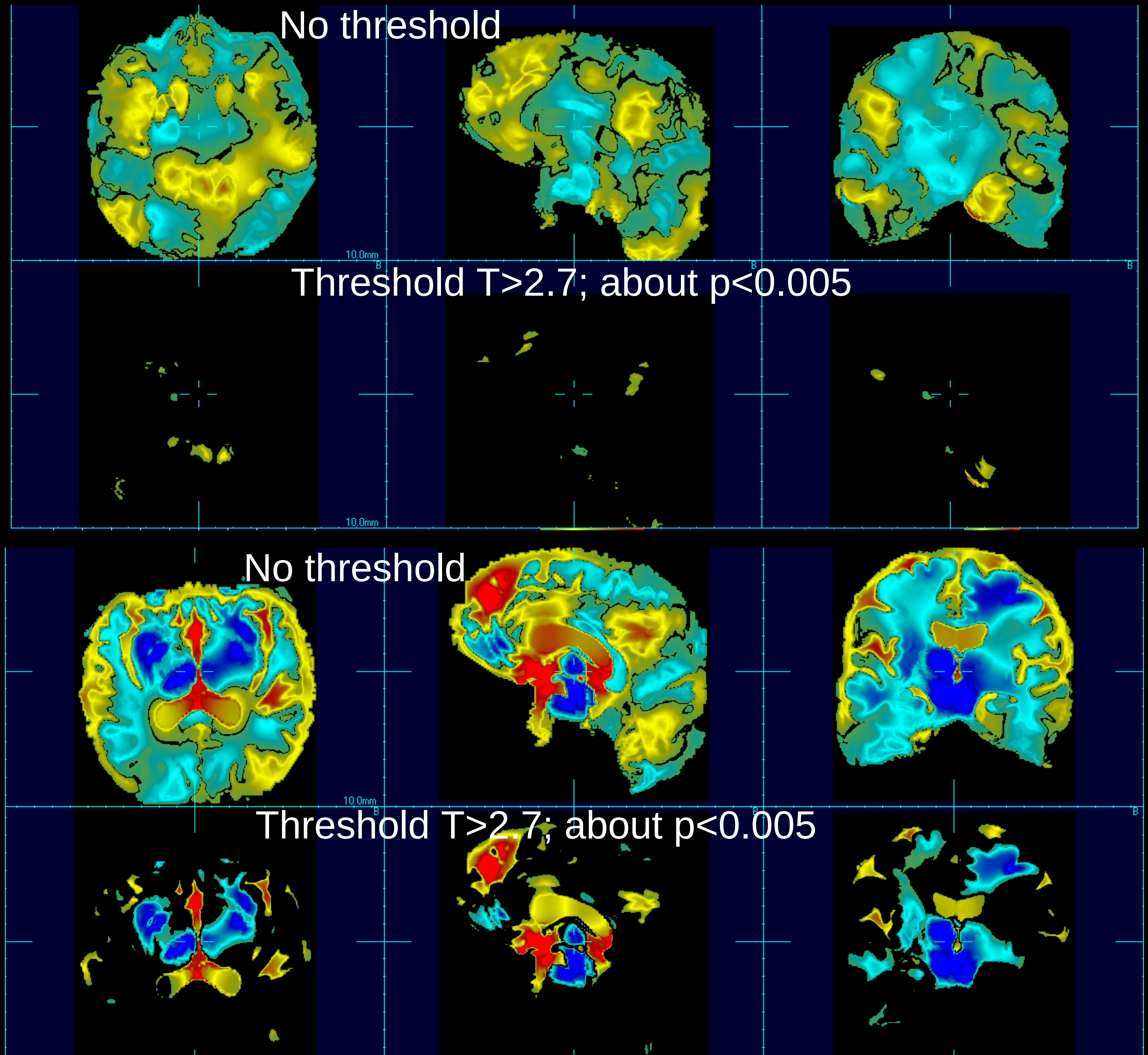
$$\begin{bmatrix} y_{11} \\ y_{21} \\ \vdots \\ y_{n1} \end{bmatrix} = \begin{bmatrix} 1 & 73 & 4 & 1 \\ 1 & 68 & 8 & 1 \\ & & \ddots & \\ 0 & 65 & 16 & 1 \end{bmatrix} \begin{bmatrix} \beta_{diag1} \\ \beta_{age1} \\ \beta_{score1} \\ \beta_{\text{int}1} \end{bmatrix}$$



t>5.4 is threshold for $p<0.05$

Cluster Analysis

- Basic idea: clusters of voxels changing in the same way are more “believable”
- Large clusters of voxels with small t-statistics more significant than isolated voxels with large t


No threshold
10.0mm
Threshold T>2.7; about p<0.005
10.0mm
No threshold
10.0mm
Threshold T>2.7; about p<0.005

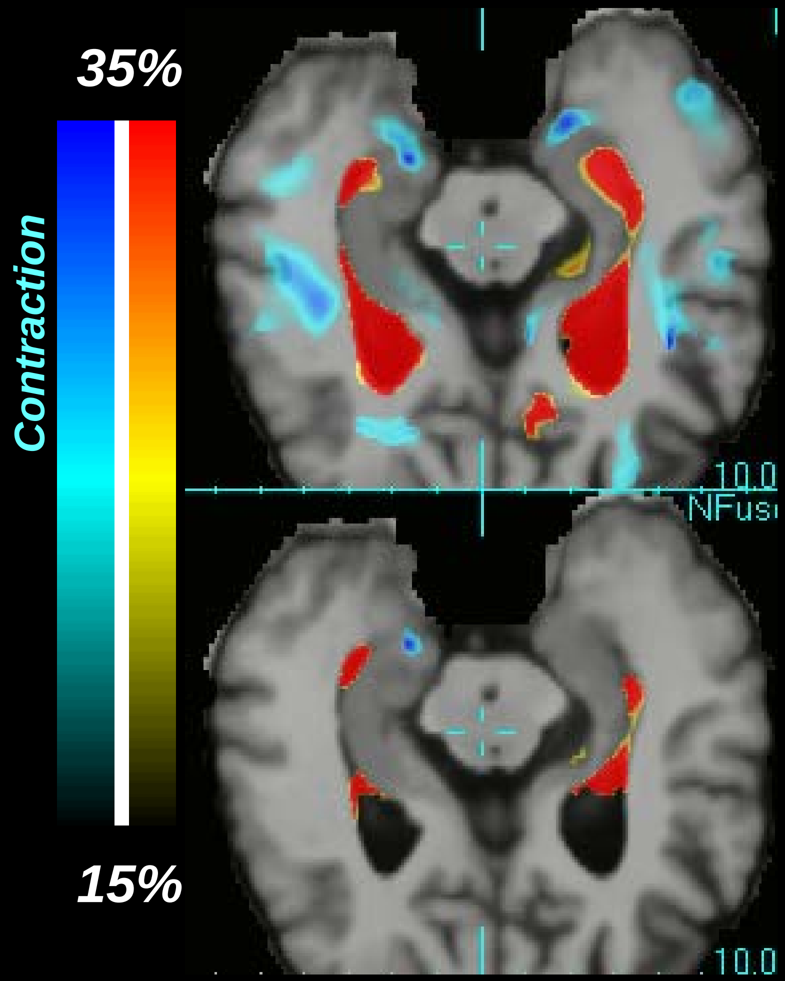
Determining Significant Clusters

- Gaussian random field analysis
  - Used in SPM
  - Kiebel et al, Neuroimage 1999, 10:756-766
  - Developed for fMRI and PET, assumptions violated in VBM and DBM
- Nonstationary gaussian random fields
  - Worsley's fMRIstat
  - Hayasaka et al, Neuroimage 2004, 22:676-687
  - SPM extensions
- Nonstationary cluster permutation methods
  - Hayasaka et al, Neuroimage 2004, 22:676-687
  - SnPM, a toolbox for SPM

False Discovery Rate

- Bonferroni, permutation testing, random field methods control the chance of any false positives
- FDR controls the expected proportion of false positives among suprathreshold voxels
- Determined from the observed p-value distribution
- More sensitive because more lenient

The Effect of Correction for Multiple Comparisons



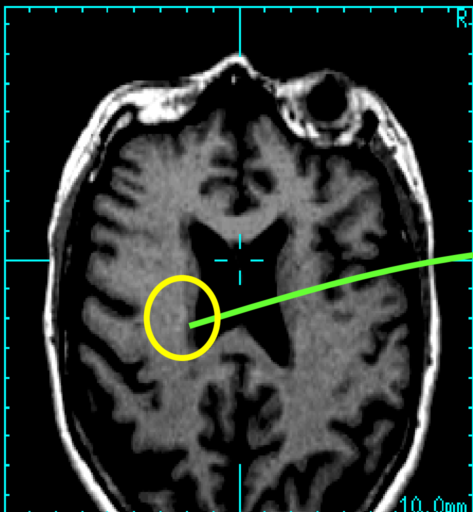
AD vs. control,
p<0.05 uncorrected

AD vs. control,
p<0.05 corrected with PT

Deformation Morphometry vs VBM

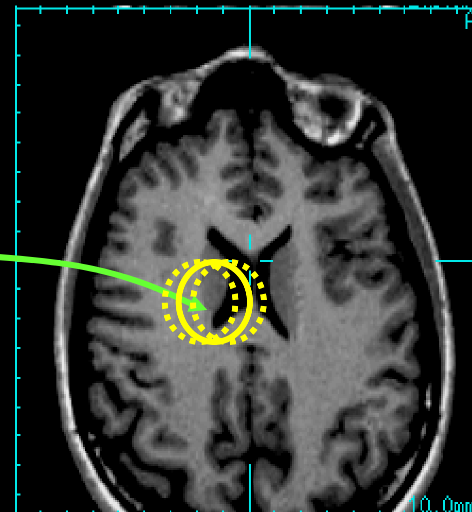
- Voxel based morphometry (VBM)
  - confuses tissue volume loss and displacement
  - relies on the automated segmentation of images
  - regions of abnormal WM may be incorrectly classified as GM
  - segmentation of subcortical structures can be problematic due to mixing of GM and WM
- VBM is a flawed method for investigating white matter (WM) loss or subcortical involvement.

Using Between Subject Registration: Computational Morphometry

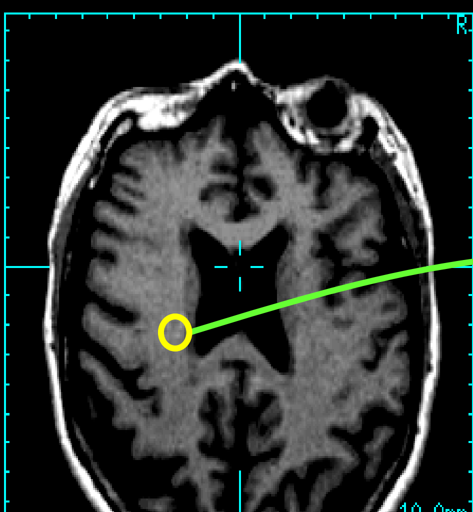


Coarse Non-Rigid Transformation

Compare Regional Stats: e.g. Gray Matter Density

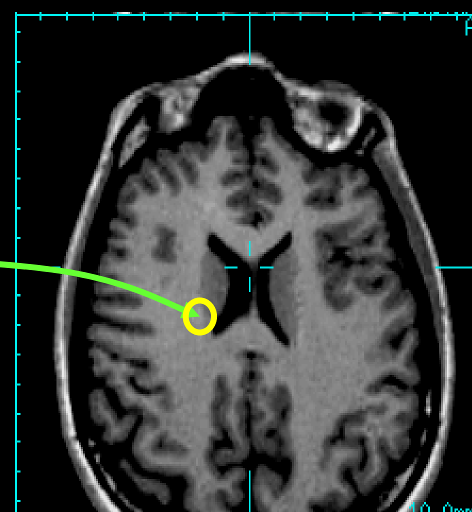


Voxel Morphometry



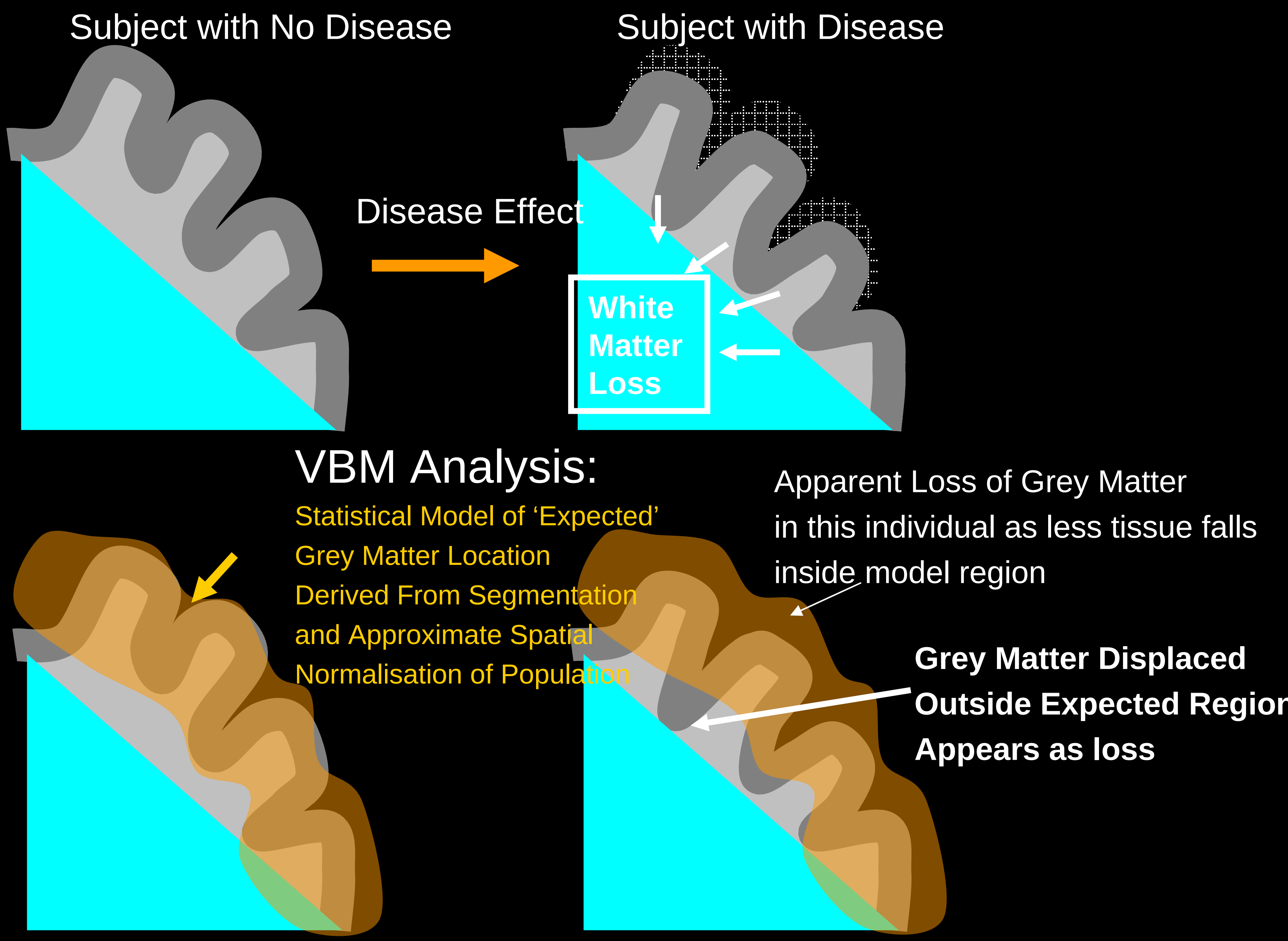
Fine+Accurate Nonlinear Transformation

Transformation Describes All Differences

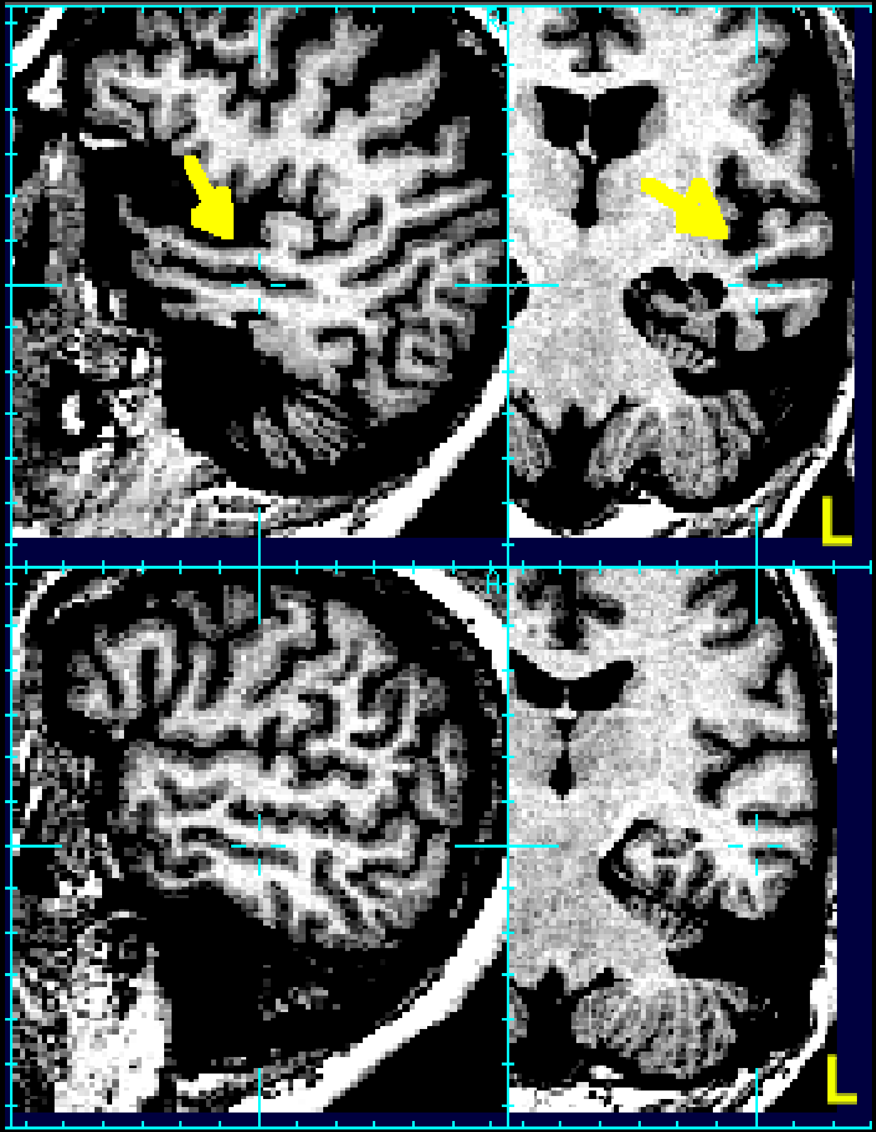


Deformation or Tensor Morphometry

Ambiguities in Interpreting VBM results

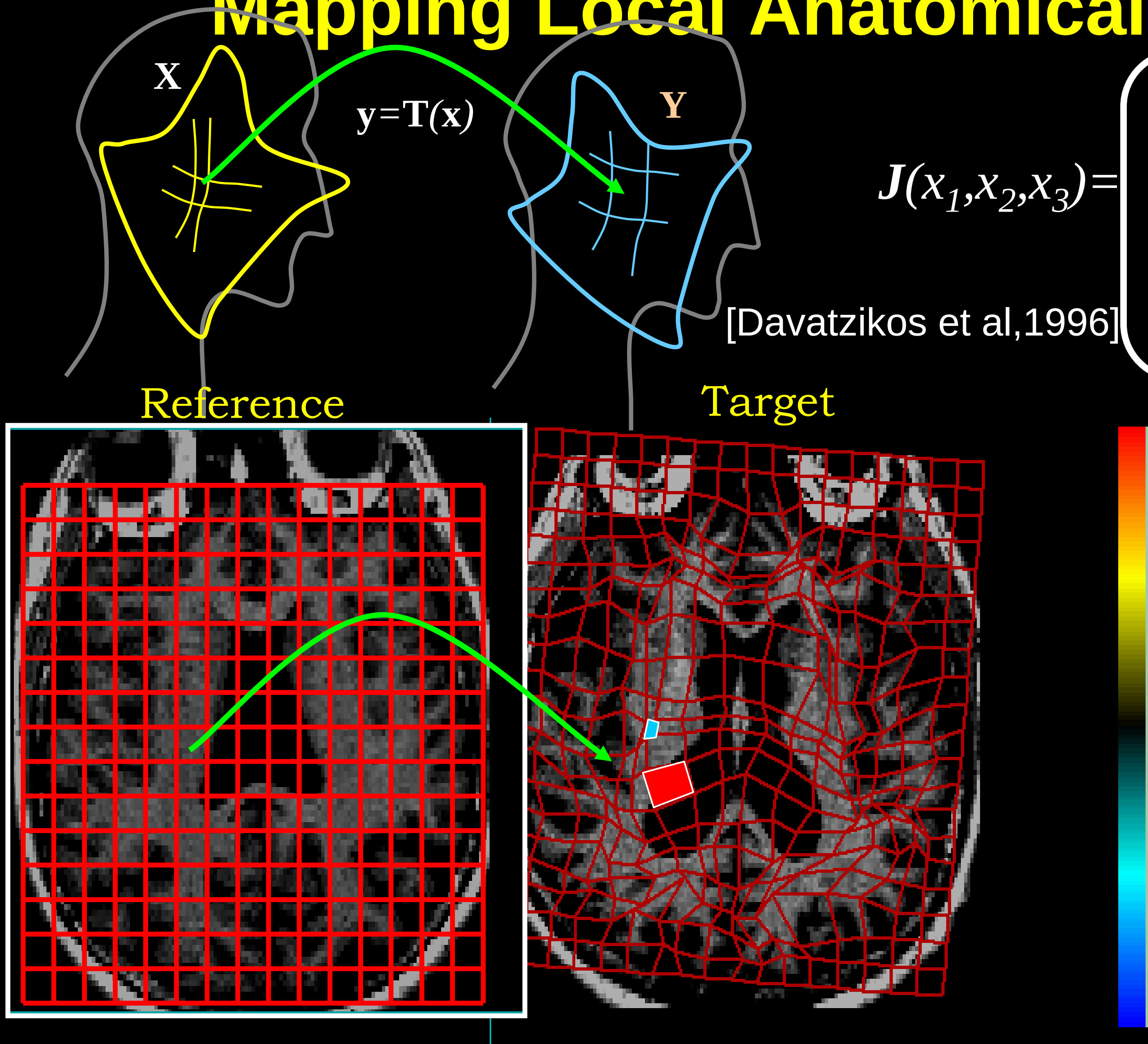


Issues with Conventional Voxel Based Morphometry



- Classical VBM: ‘Measurement by residual Misregistration’
  - Differences in Regional GM/WM after approximate spatial normalisation
- Tissue Displaced by loss of neighboring tissues can appear as ‘Lost’ Tissue

3D Deformation Tensor Morphometry: Mapping Local Anatomical Size



$$J(x_1,x_2,x_3)=\begin{pmatrix} \frac{dy_1}{dx_1} & \frac{dy_1}{dx_2} & \frac{dy_1}{dx_3} \\ \frac{dy_2}{dx_1} & \frac{dy_2}{dx_2} & \frac{dy_2}{dx_3} \\ \frac{dy_3}{dx_1} & \frac{dy_3}{dx_2} & \frac{dy_3}{dx_3} \end{pmatrix}$$

[Davatzikos et al,1996]

$$\left| \frac{\partial y}{\partial x} \right|$$

Group Comparisons of Between Subject Differences using Deformation Morphometry

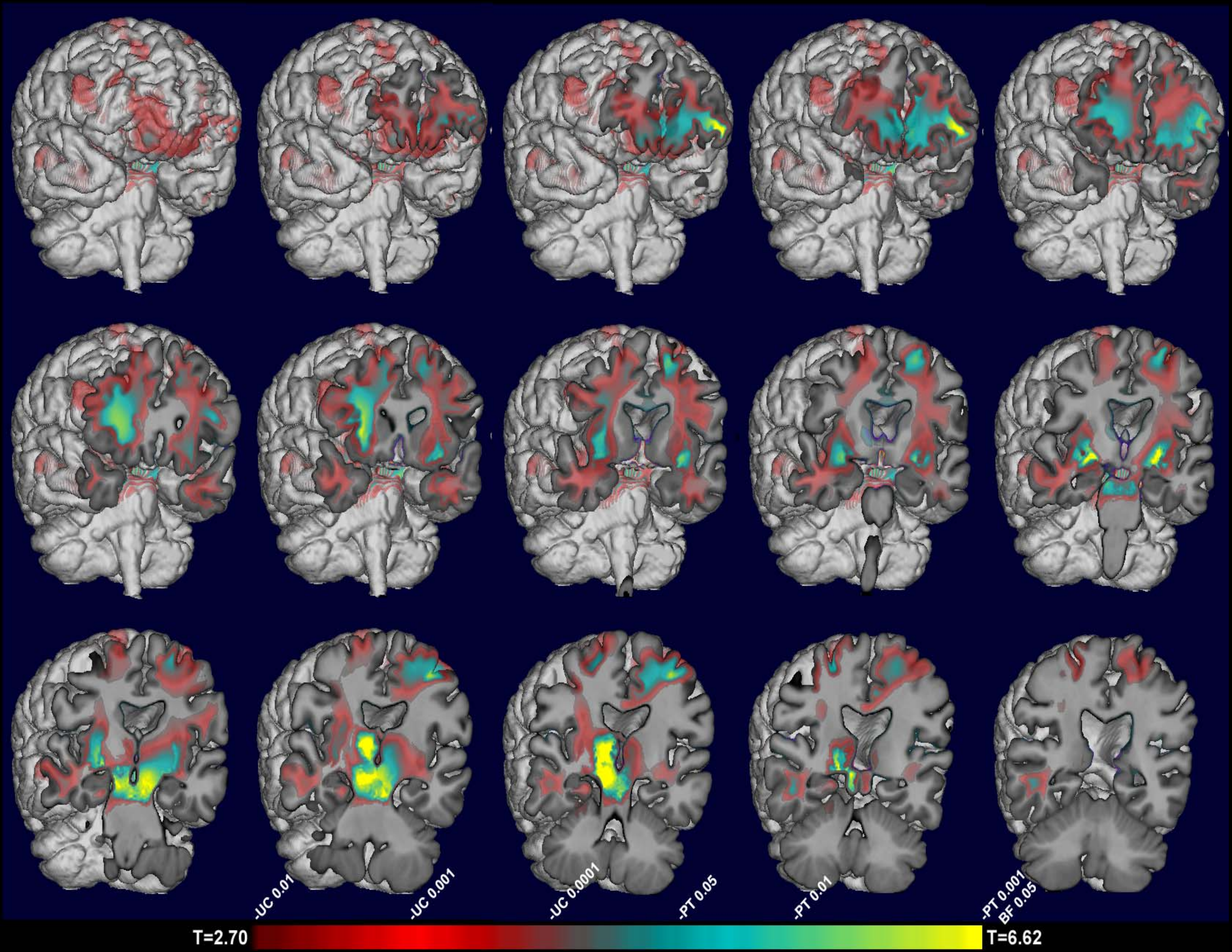
FTD

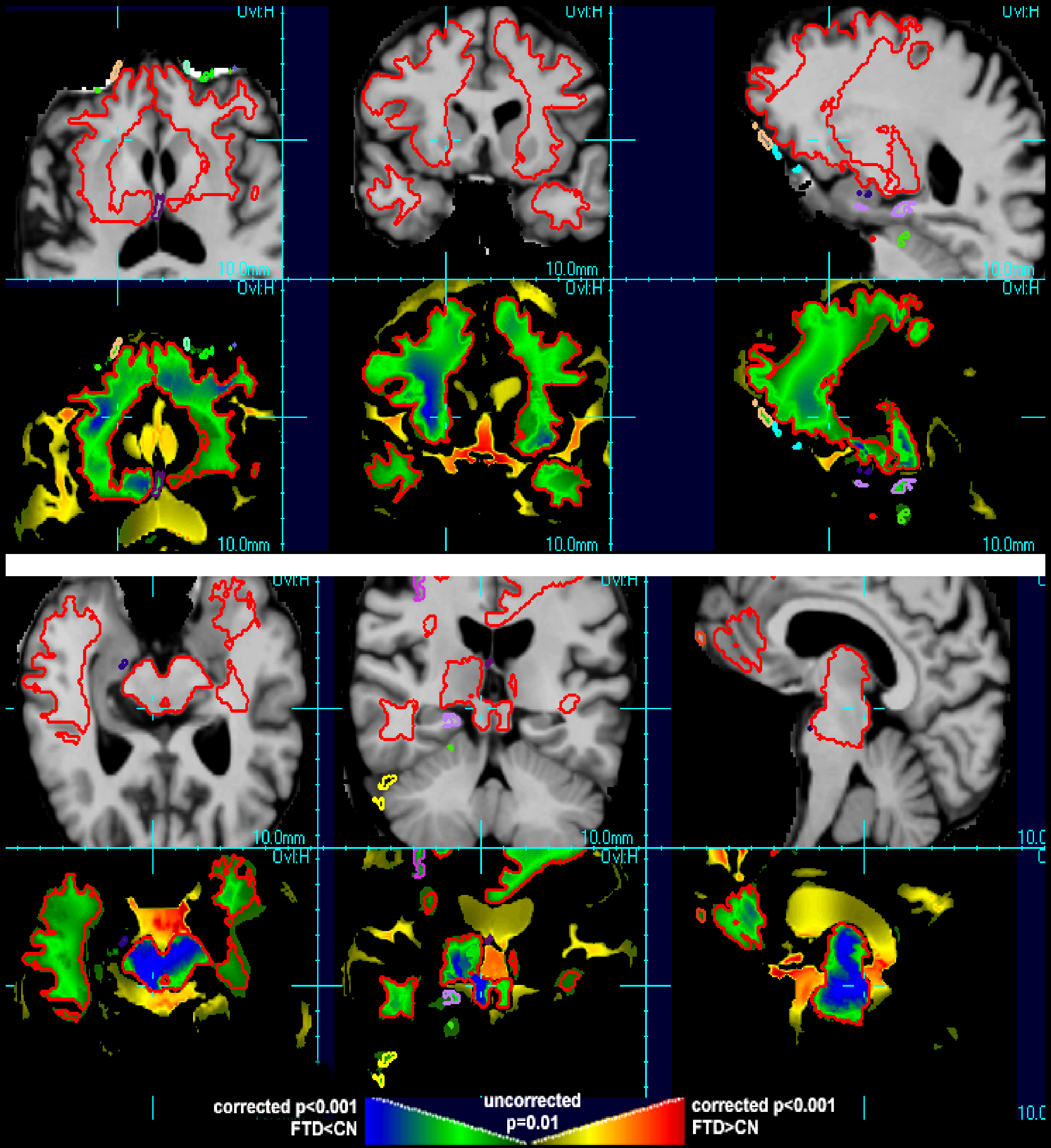
- Clinical subtype of frontotemporal lobar degeneration
- Impairment of personal conduct and social behavior
- Sometimes presents with ALS
- Postmortem studies show that atrophy:
  - begins in frontal lobe,
  - extends into the anterior temporal lobes and basal ganglia,
  - eventually involves subcortical structures,
  - white matter is prominently affected.

Methods

	Age	CDR	MMSE
CN (N=22)	63 ± 7	0	29.3 ± 2.2
FTD (N=22)	63 ± 6	1.12 ± 0.69	23.1 ± 7.0

- Deformation maps created from baseline MRI
- Dependent variables were deformation maps
- Independent variables: group and head size

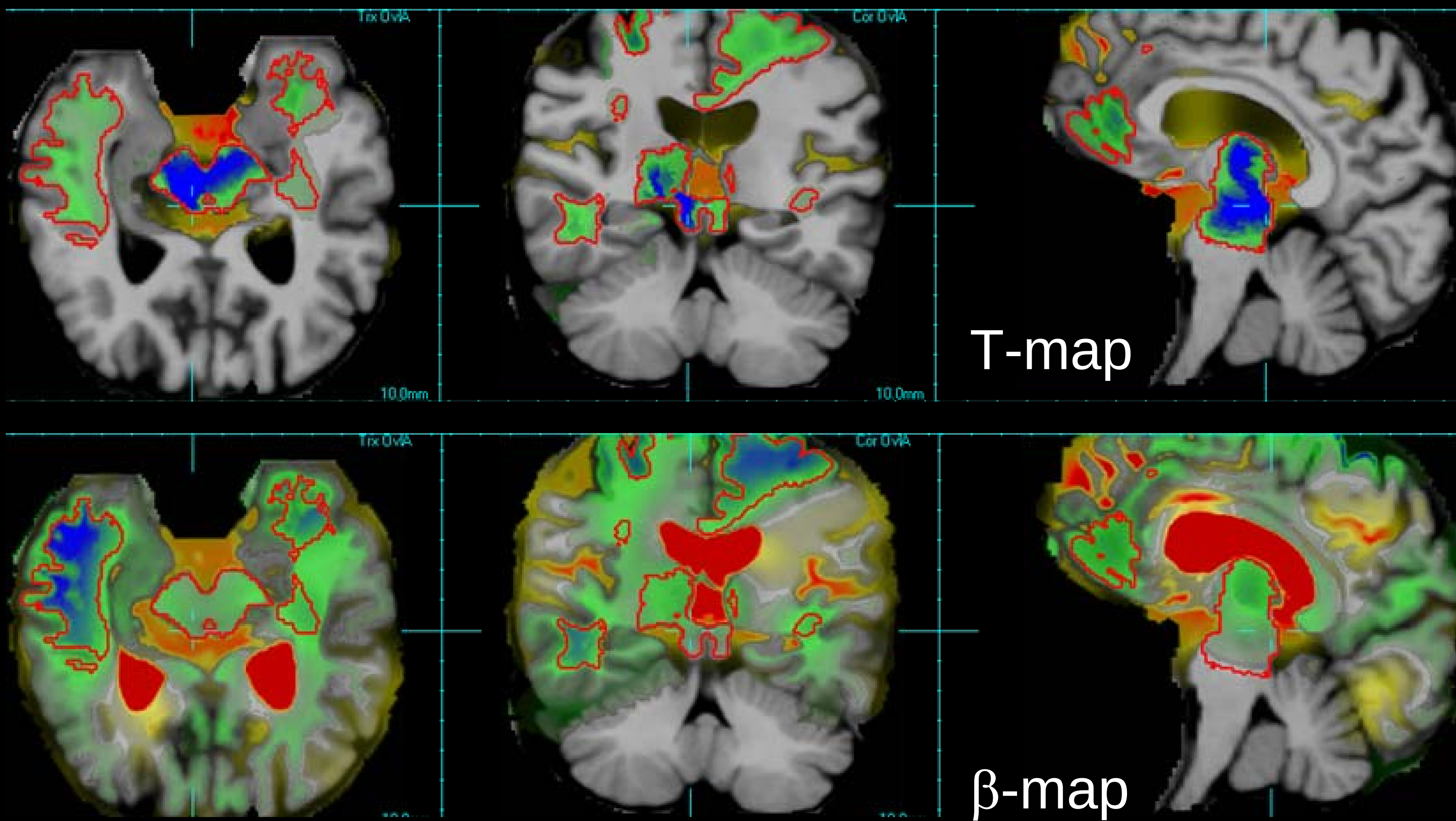

-UC 0.01
-UC 0.001
-UC 0.0001
-PT 0.05
-PT 0.01
-PT 0.001
BF 0.05
T=2.70
T=6.62



10.0mm
corrected p<0.001
FTD<CN
uncorrected
p=0.01
corrected p<0.001
FTD>CN

Don’t Forget to Examine the Map of Estimated Effects!

ROI Estimates in Voxel Morphometry



1-50% contraction/expansion

Magnitude of Atrophy

We observed tissue reductions of:

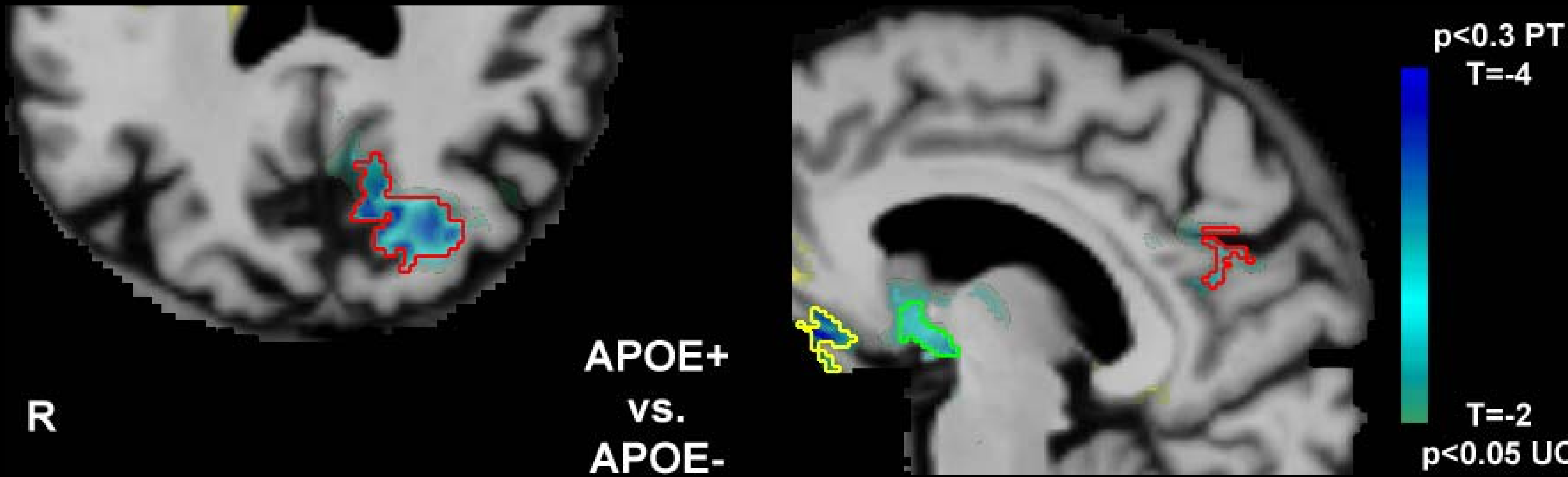
- 34% in the ventromedial frontal region
- 26% in the thalamic region
- 10% in the brainstem region
- 35% in the temporal region (not as significant)
  - Could be poor alignment of structures
  - Inconsistent spatial pattern of atrophy, consistent with considerable variability of clinical features of FTD
- No significant atrophy of parietal or occipital lobes

Validation:
ROI Volumes on 10 FTD vs 10 CN

	CN	FTD	%Reduction	p-value
%Frontal Lobe	34.5 ± 1.0	31.9 ± 2.27	7.5	0.003
%Temporal Lobe	16.3 ± 1.0	16.3 ± 1.0	0	0.85
%Brainstem midsagittal	0.086 ± 7.65E-05	0.076 ± 7.46E-05	11.6	0.006

Volumes expressed as % of intracranial volume

25 APOE ε4-Positive vs. 36-Negative (all subjects impaired)



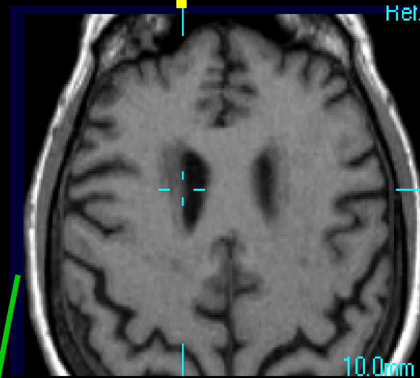
PET studies report reductions in posterior cingulate; frontal reductions consistent with reports of accelerated conversion to dementia in APOE ε4 positive subjects.

Group Differences of Within Subject Changes for Longitudinal Studies

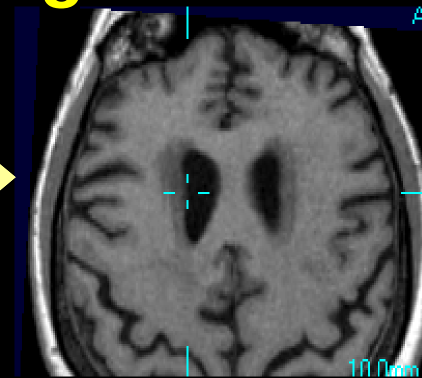
Deformation Morphometry

Creation of Maps of Longitudinal Deformation

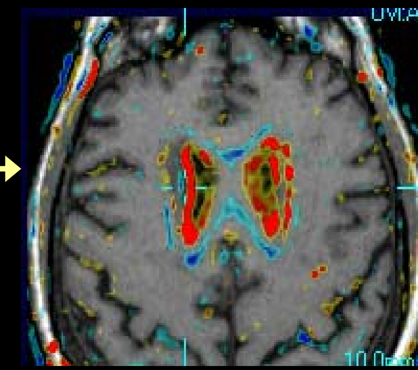
Step 1: Within subject registration between timepoints



timepoint 1

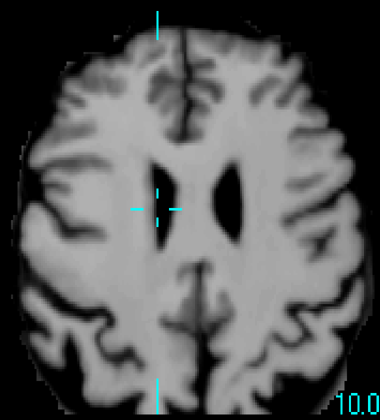


timepoint 2



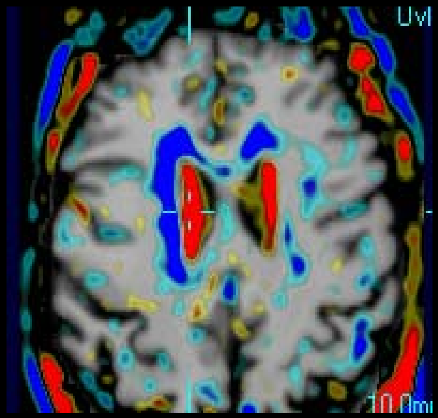
atrophy rate map

Step 2: Subject to atlas registration



atlas

Step 3: Combine registrations



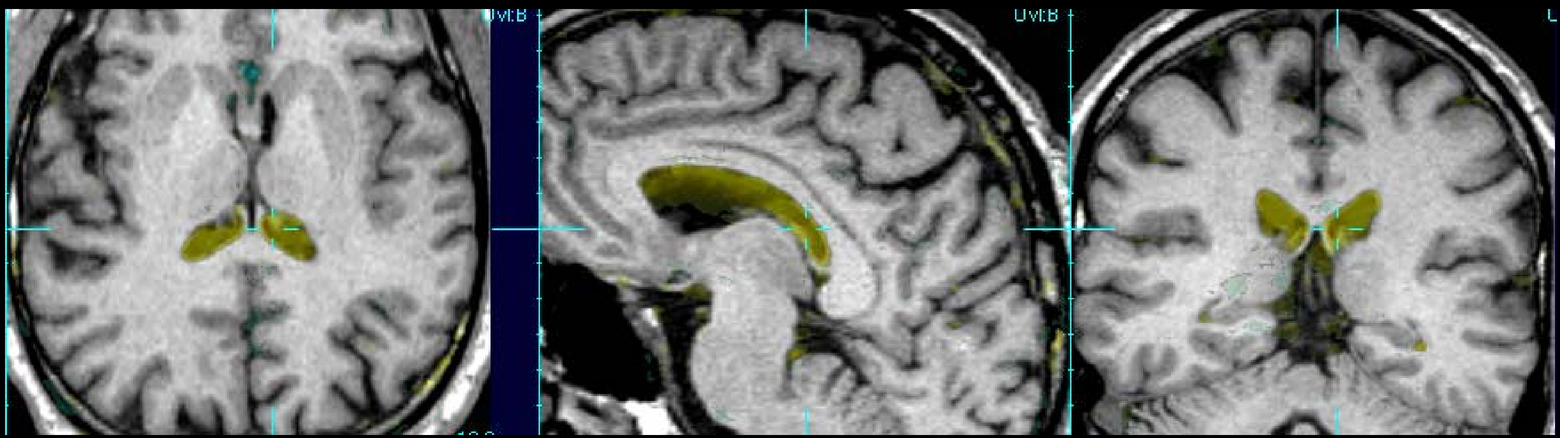
deformation map: atrophy rate in common space

PTSD Question

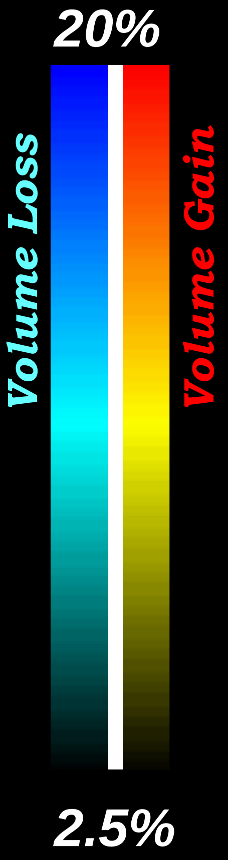
- Samuelson reported greater cognitive decline in PTSD
  - Delayed facial recognition (WMS-III Faces II)
  - Working memory (Digit Span)
- Is there progressive brain shrinkage with PTSD?
- Longitudinal images and neuropsychological data were analyzed to:
  - Determine the extent to which PTSD accelerates brain atrophy

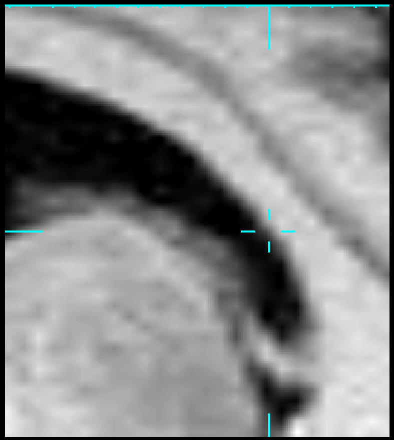
Example PTSD-

Interscan Interval 4.1 yrs

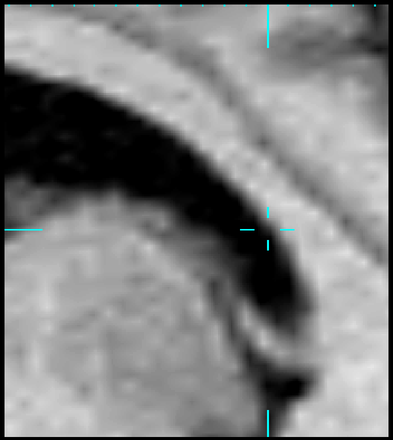


atrophy rate map





timepoint 1

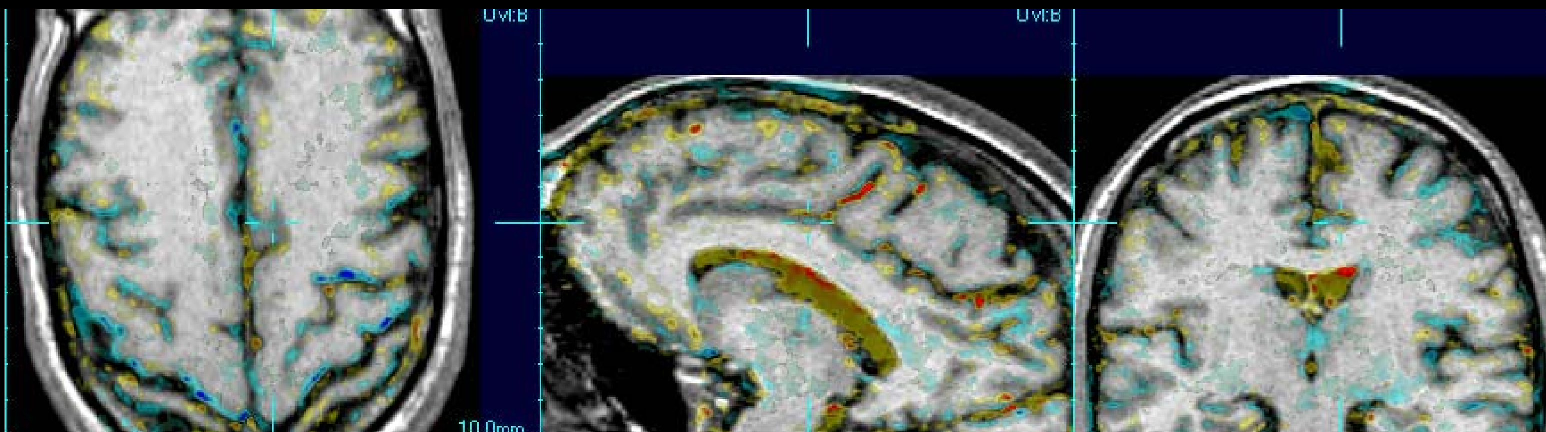


timepoint 2

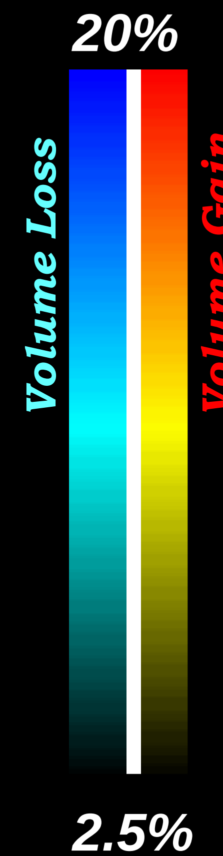
atrophy rate map

Example PTSD+

Interscan Interval 3.9 yrs

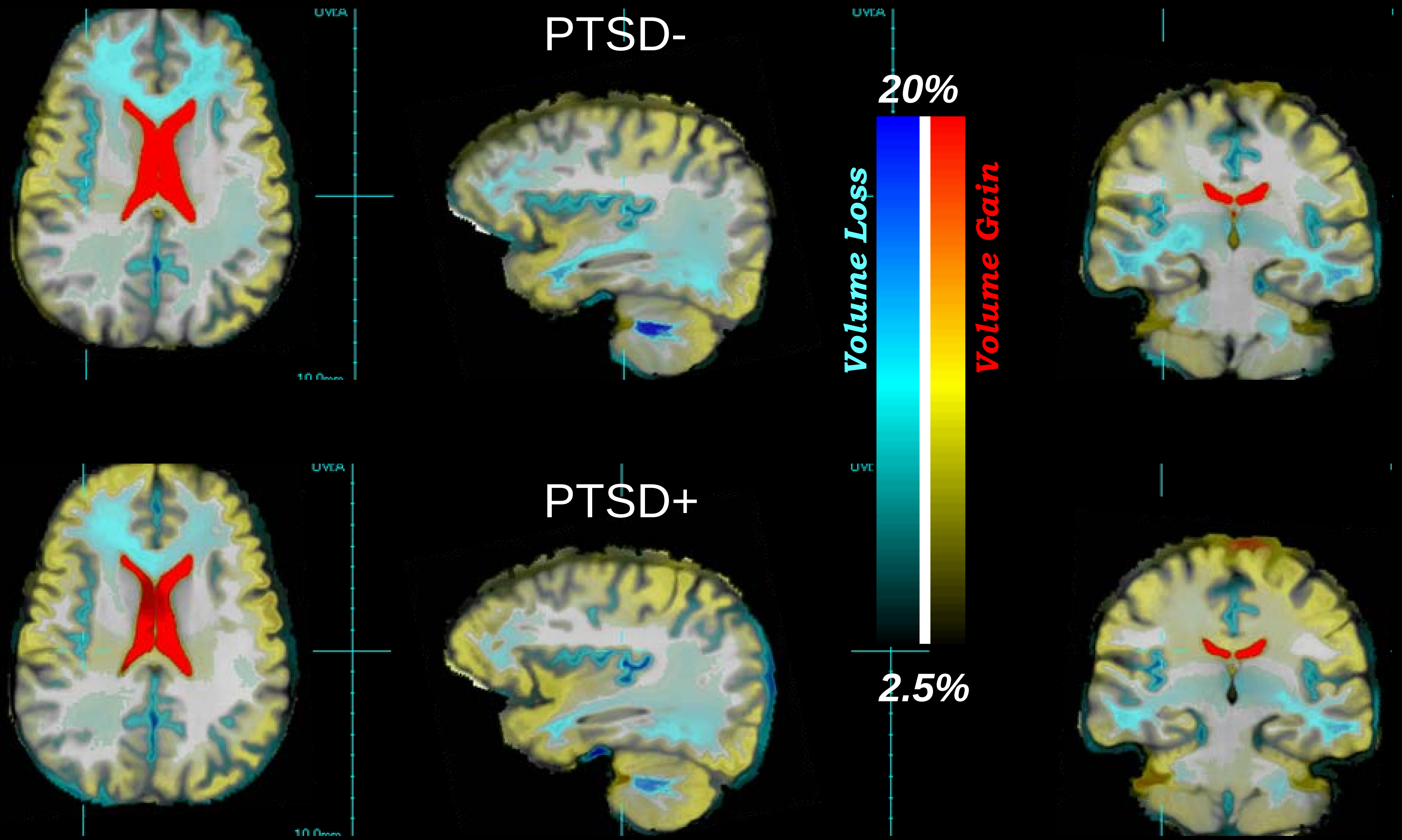


atrophy rate map

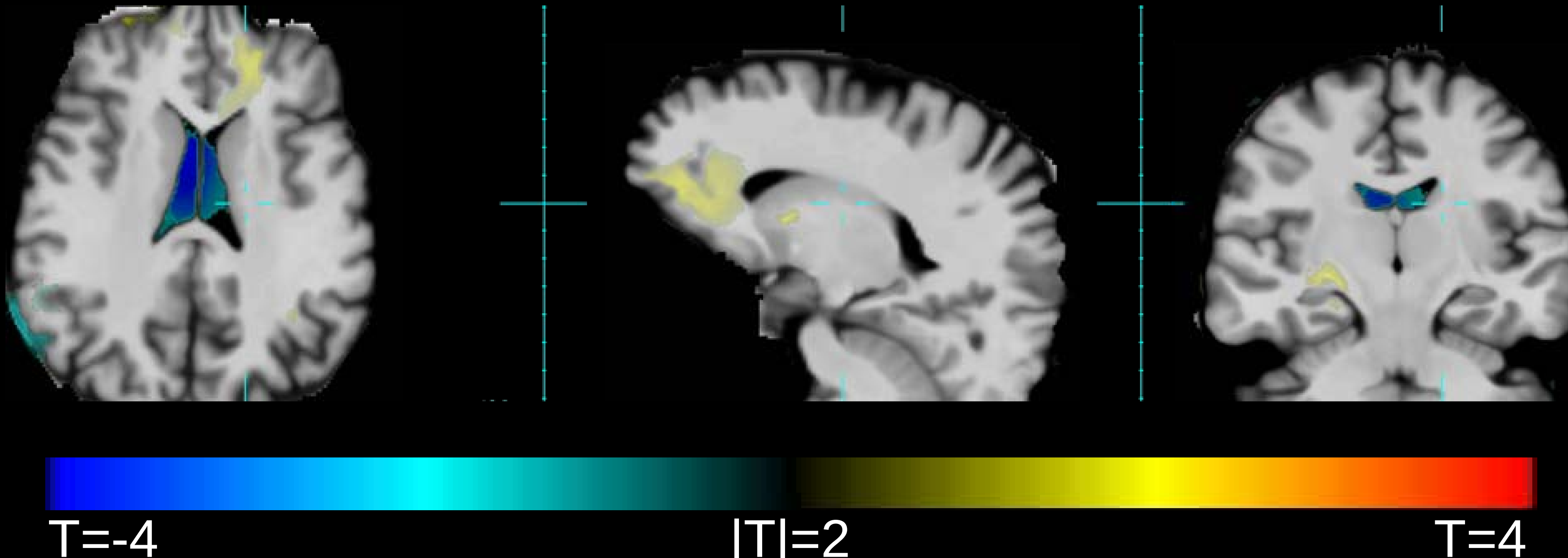


timepoint 1 | timepoint 2 | atrophy rate map

Average Rate of Atrophy



PTSD- vs. PTSD+
Map of T-statistics

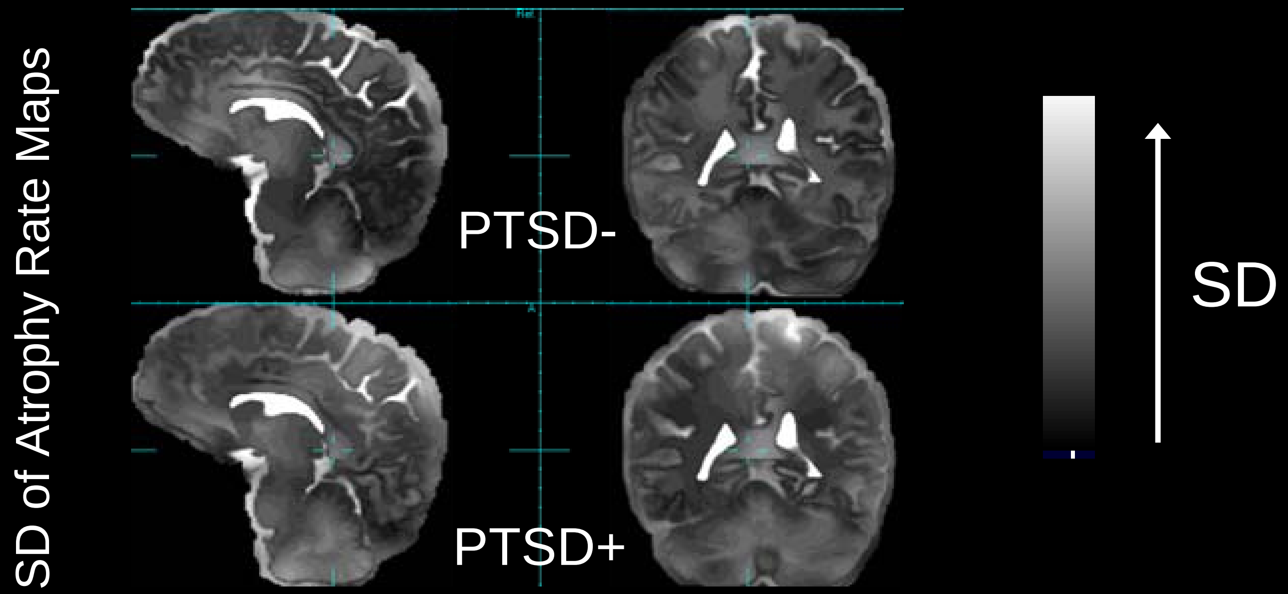


Yellow shows regions of slower brain aging in PTSD+ patients
Blue shows regions of faster brain aging in PTSD+ patients

Small regions of low significance showing opposite effects from expected!

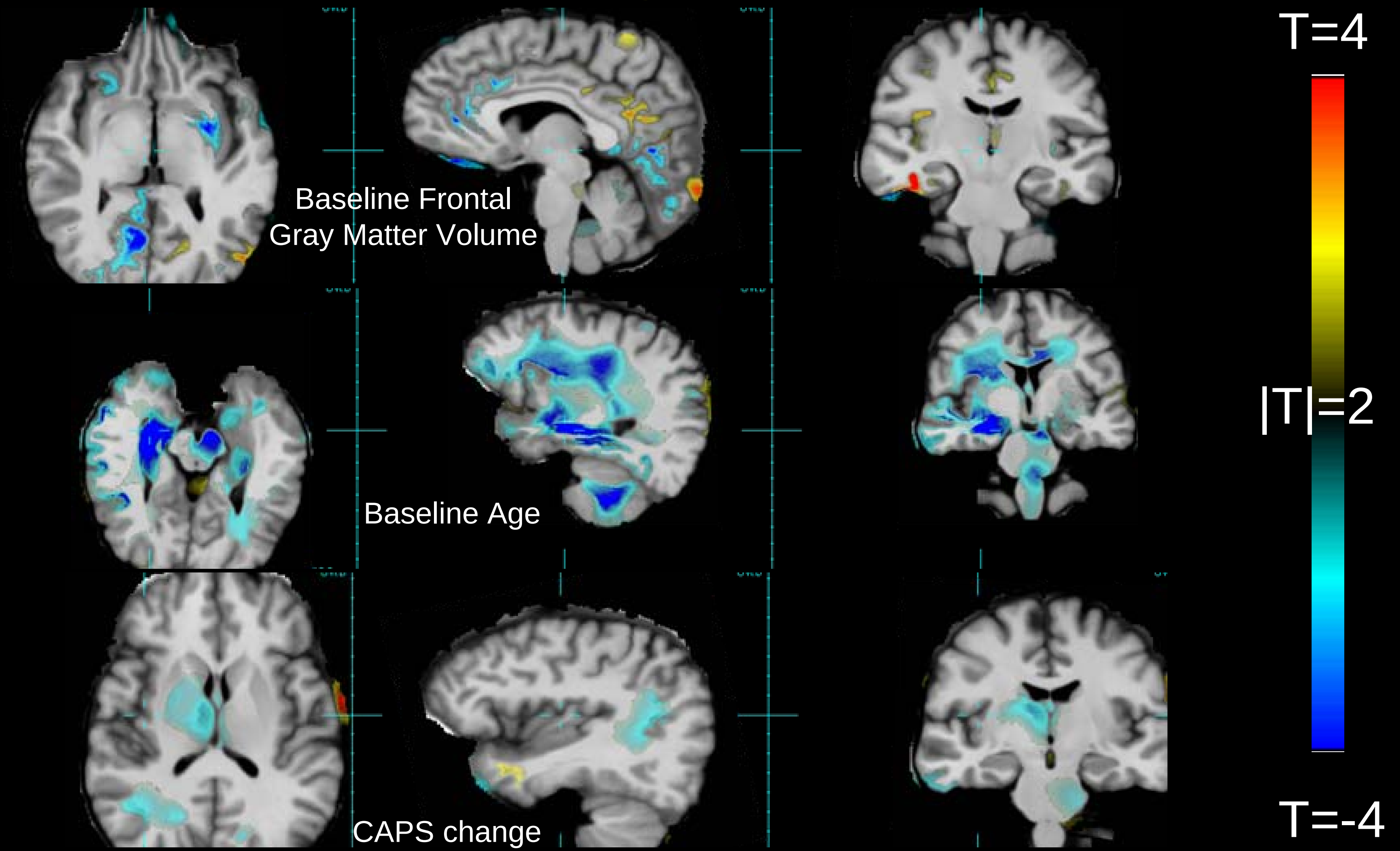
What next?

- Must be greater variability in atrophy rates among PTSD+



- Can we determine measures associated with atrophy rate, account for variability, see PTSD effect?

Atrophy Rate Predictors in PTSD+

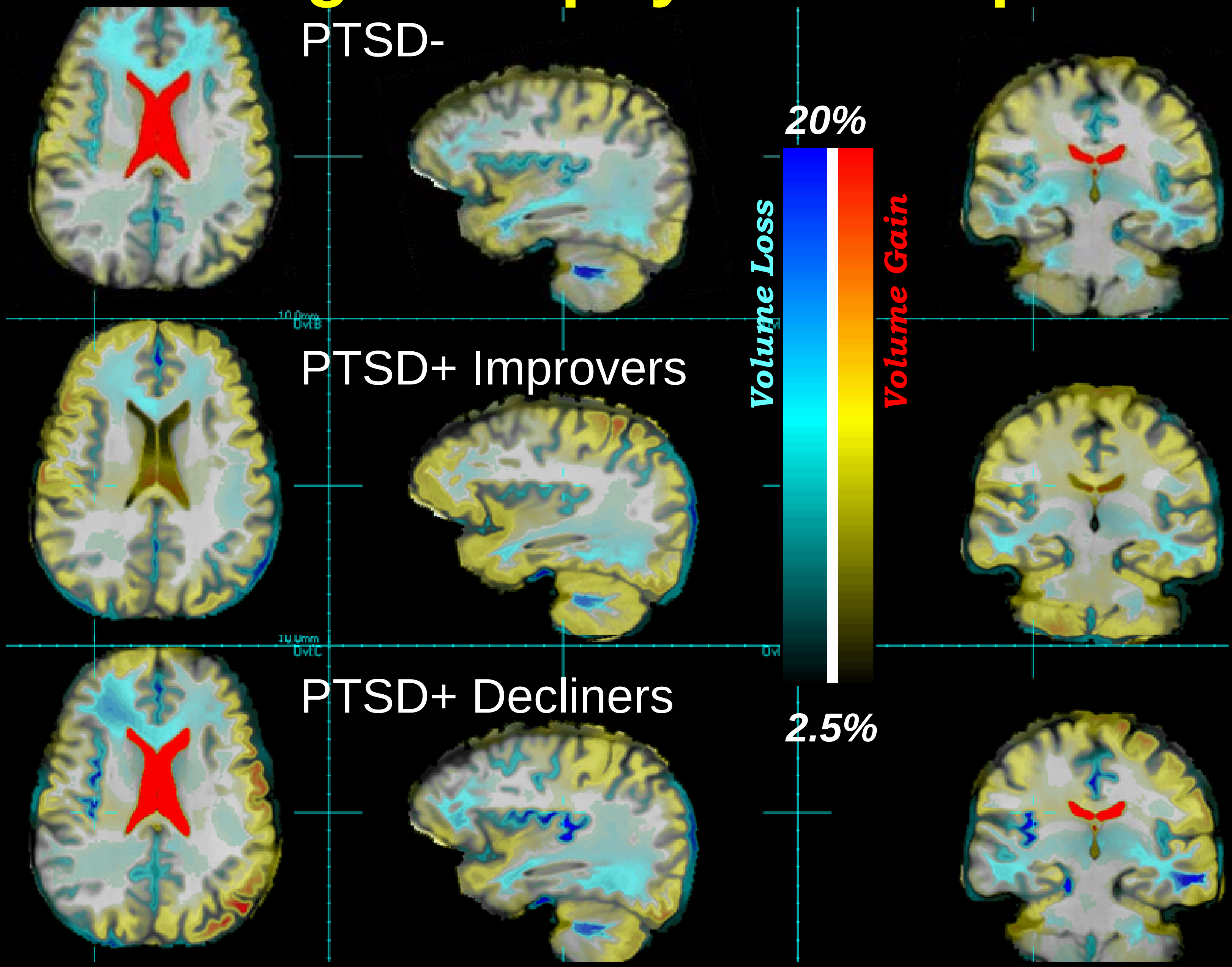


Blue: ↑volumes, ↑age, or ↑ΔCAPS associated with greater atrophy

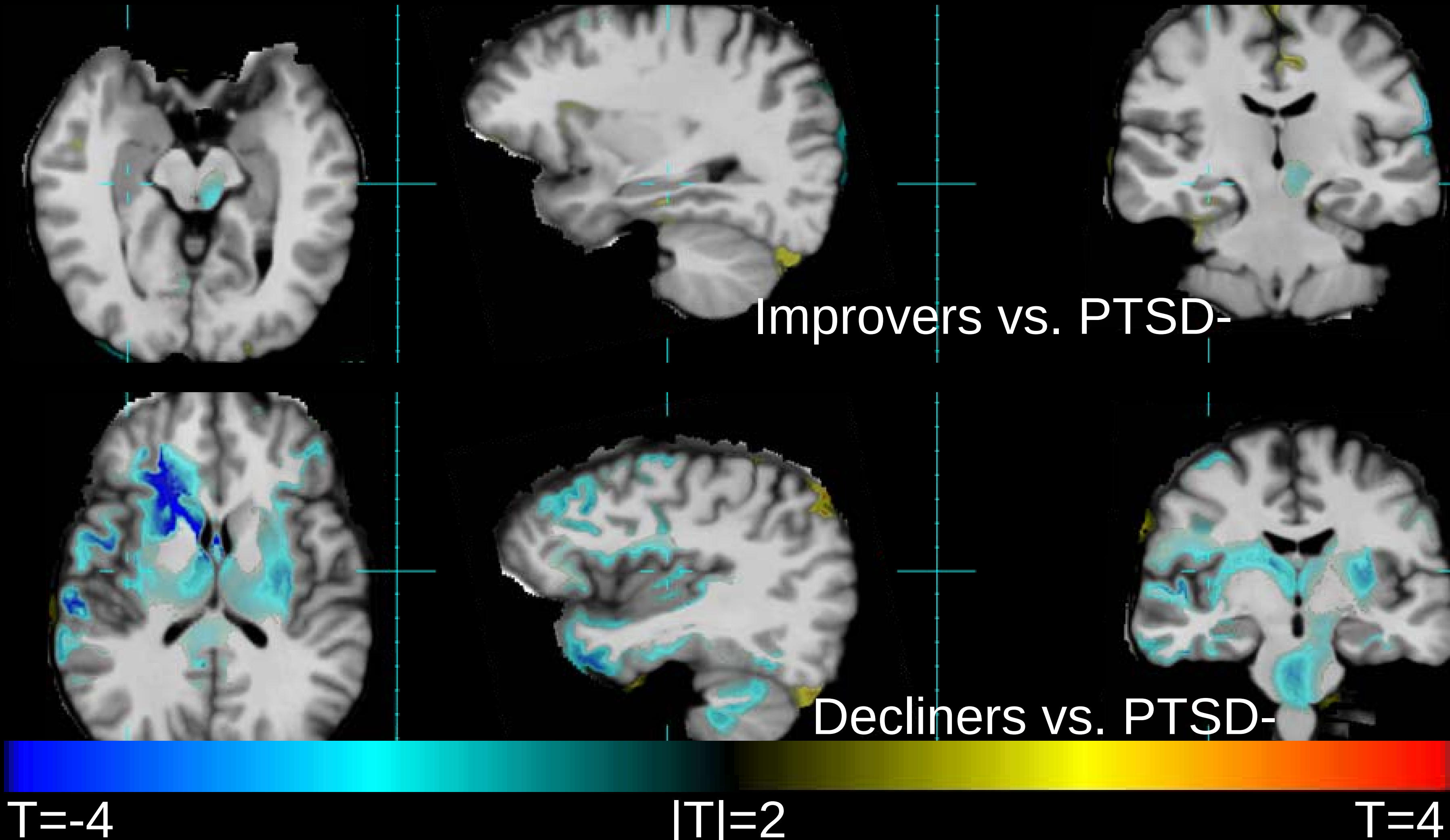
Change in CAPS

- Although all patients still diagnosed as PTSD+ at followup
  - Large variation in course of disease
  - 47 point CAPS increase to 40 point CAPS decrease
  - 6 patients went from full to partial diagnosis
- Subgroup
  - 11 Improvers had 15-40 point CAPS decrease
  - 5 Stable subjects had 6-14 point CAPS decrease
  - 9 Decliners had 2-47 point CAPS increase
- Compare Improvers and Decliners to PTSD- covarying for baseline FGM and age

Average Atrophy Rate Maps



Group Effects



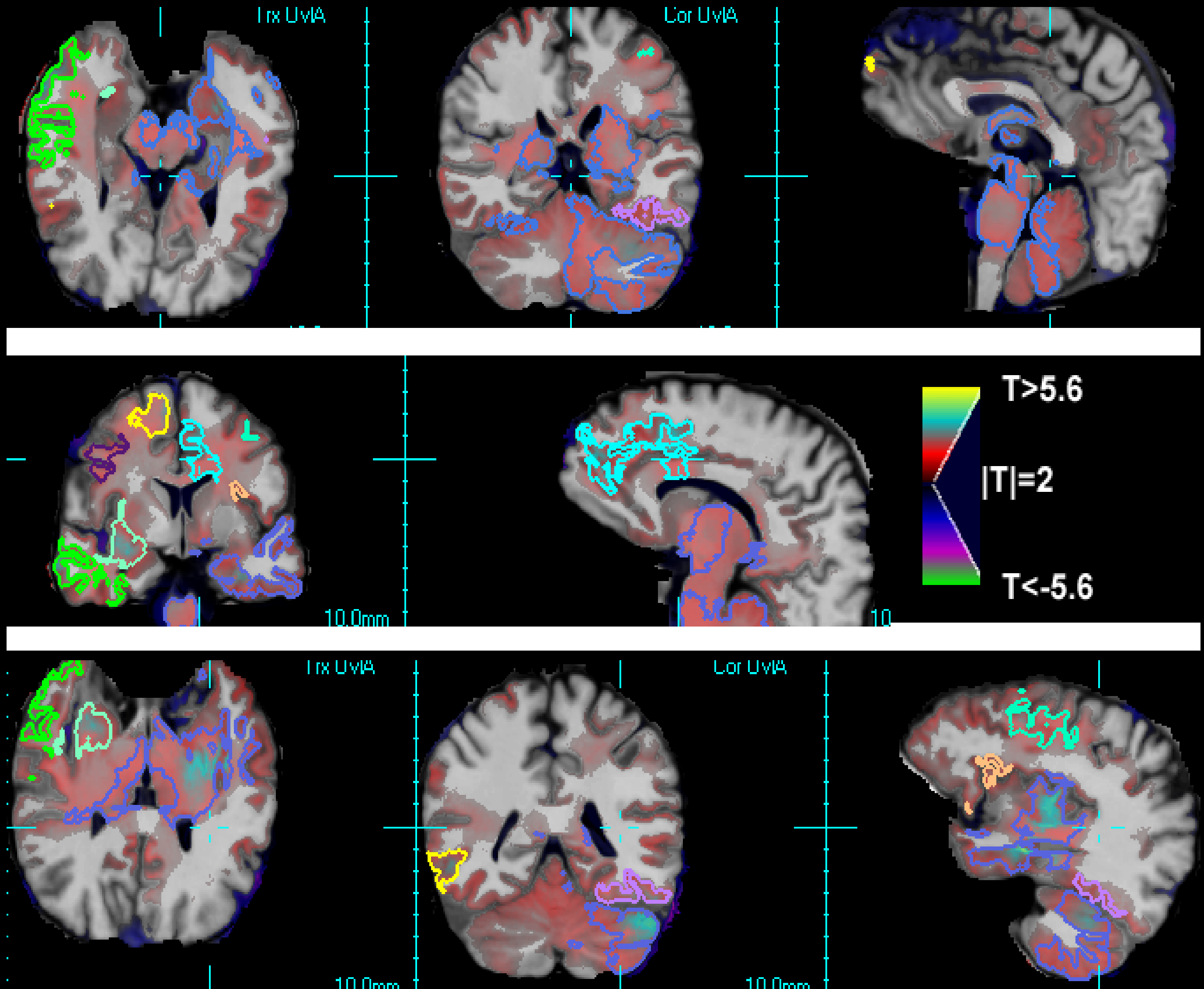
Blue: Regions of greater atrophy rate associated with group membership

Alcoholics During Abstinence

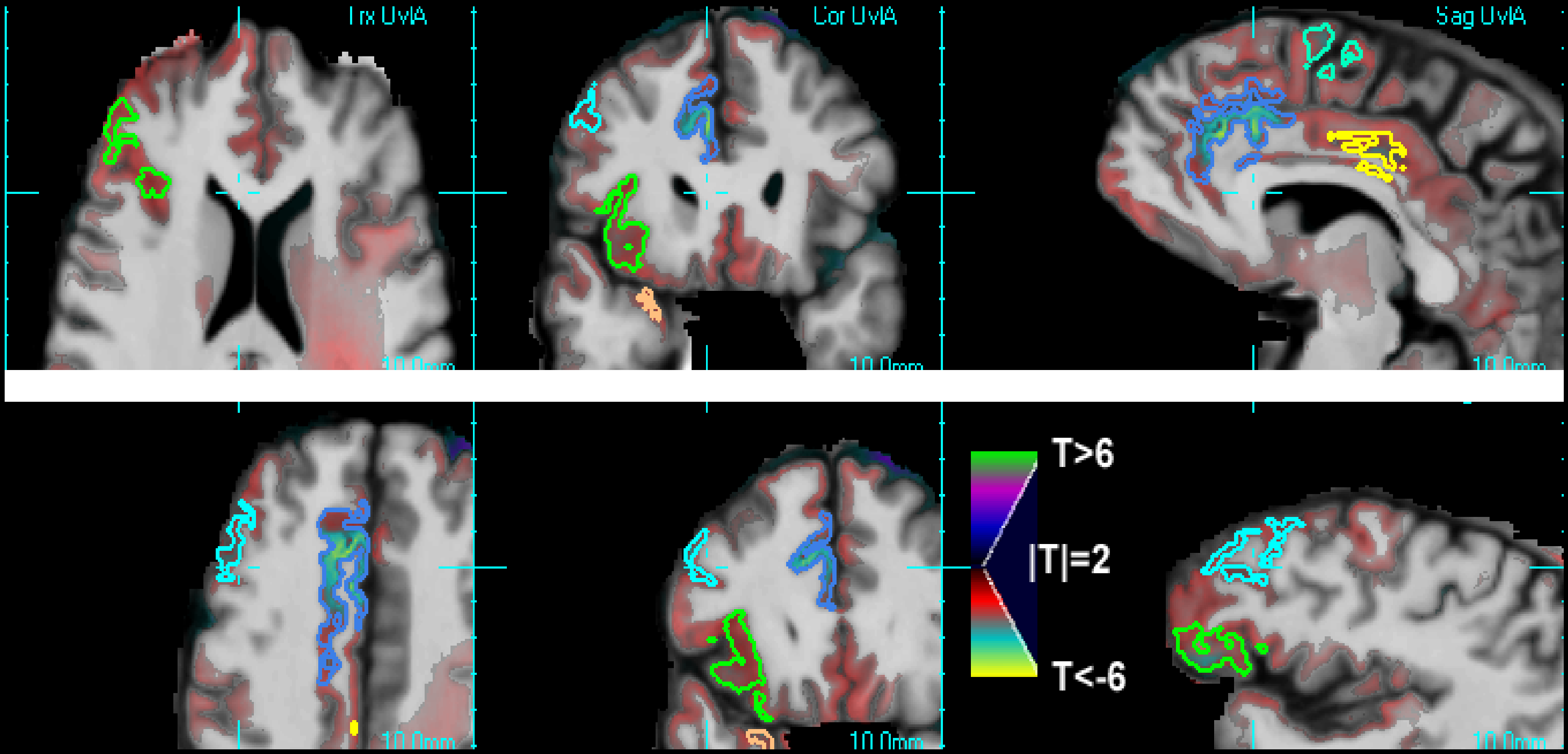
	LD N=18	RA N=47
Age [years]	45 ± 8	49 ± 14
Education* [years]	17 ± 2	14 ± 2
1 yr Avg drinks/mo*	11 ± 10	403 ± 189
Lifetime Avg drinks/mo*	17 ± 14	240 ± 123
Lifetime kg of Alcohol*	75 ± 61	1251 ± 783

*RA>LD, $p<0.001$

17 Abstainers vs 8 Relapsers



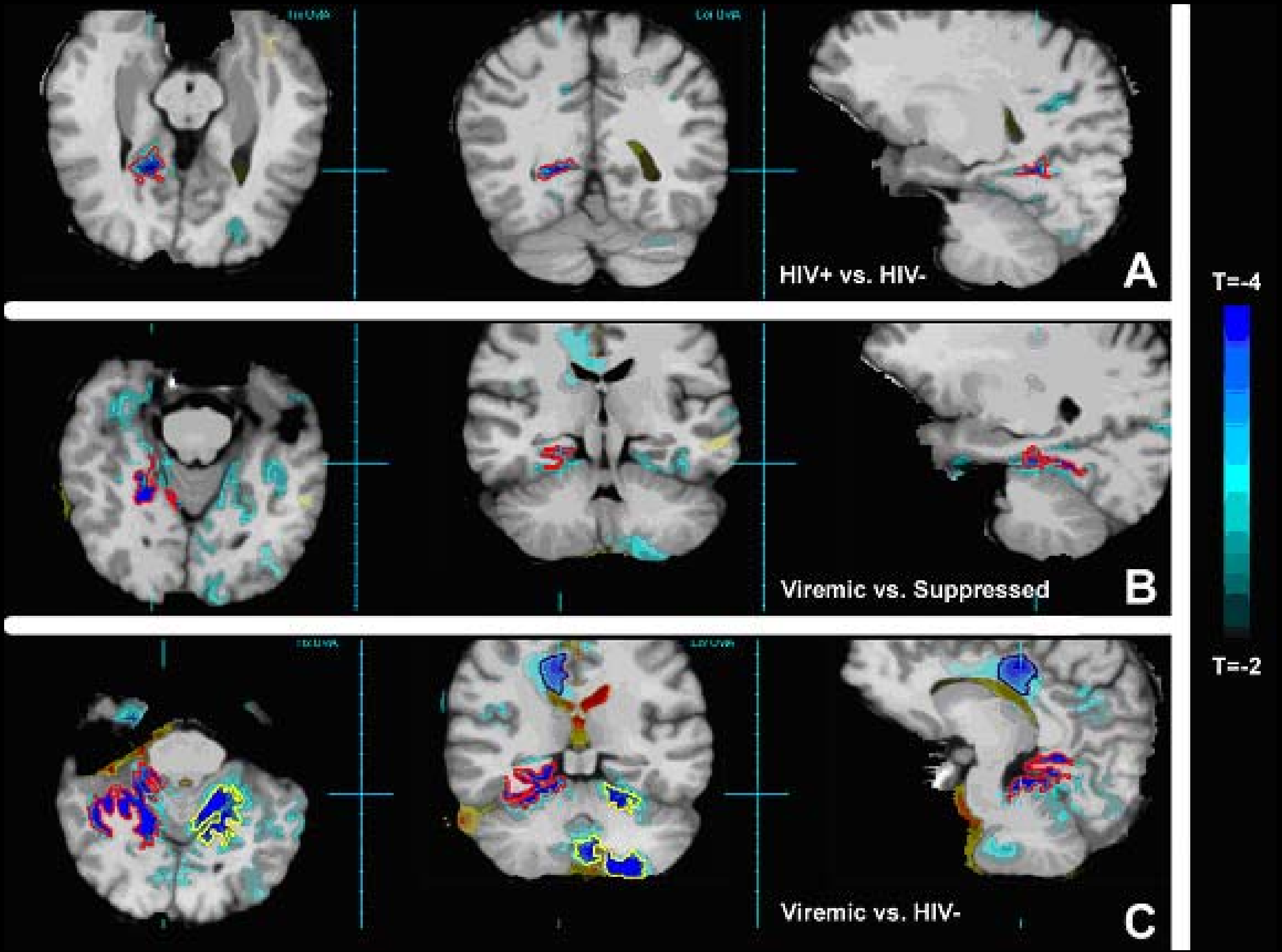
Recovery Associated with Baseline GM Volume



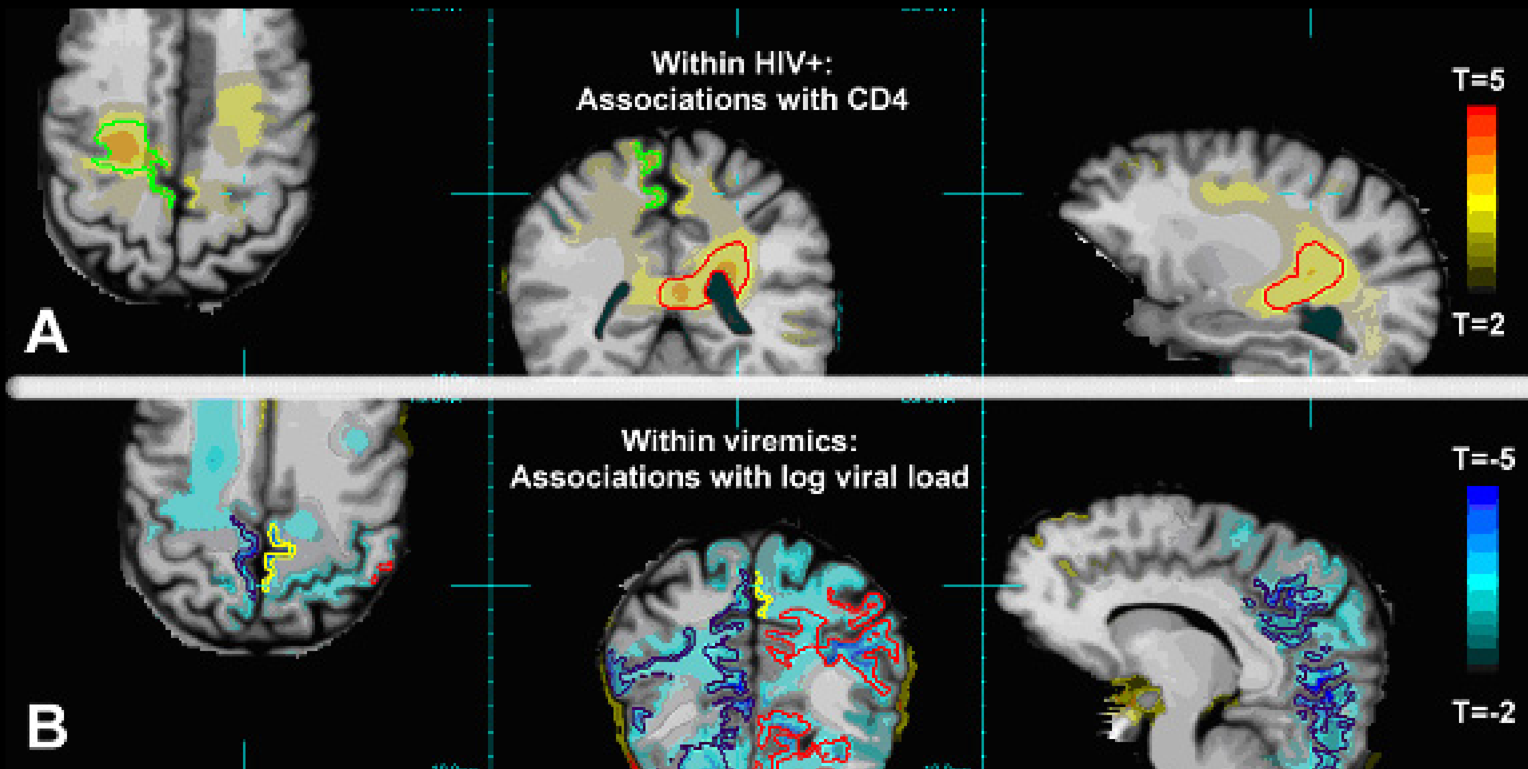
Progression of HIV

	N	Baseline Age	Baseline Log Viral Load	Baseline CD4	Baseline Current Drinks/Mo*
HIV-	30	42.3 ± 9.1	0 ± 0	765 ± 255	10 ± 11
HIV+	39**	45.0 ± 6.7	2.59 ± 1.37	396 ± 205	11 ± 17
Suppressed	21	44.2 ± 7.6	1.70 ± 0.42	432 ± 208	10 ± 13
Viremic	13	46.4 ± 5.7	4.10 ± 1.03	339 ± 195	13 ± 24

Ongoing Volume Loss in HIV Despite Treatment



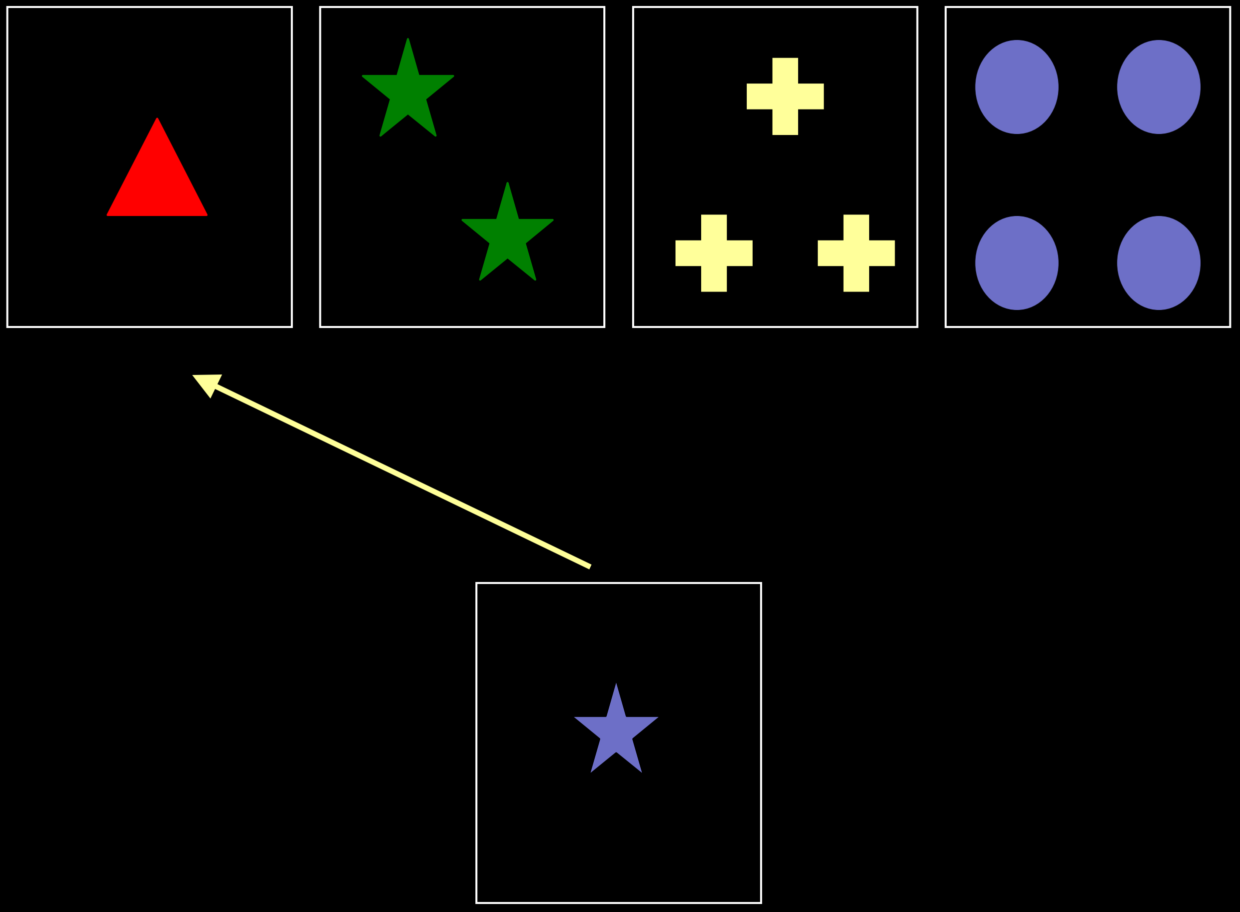
Volume Loss Associated with Baseline Clinical Variables



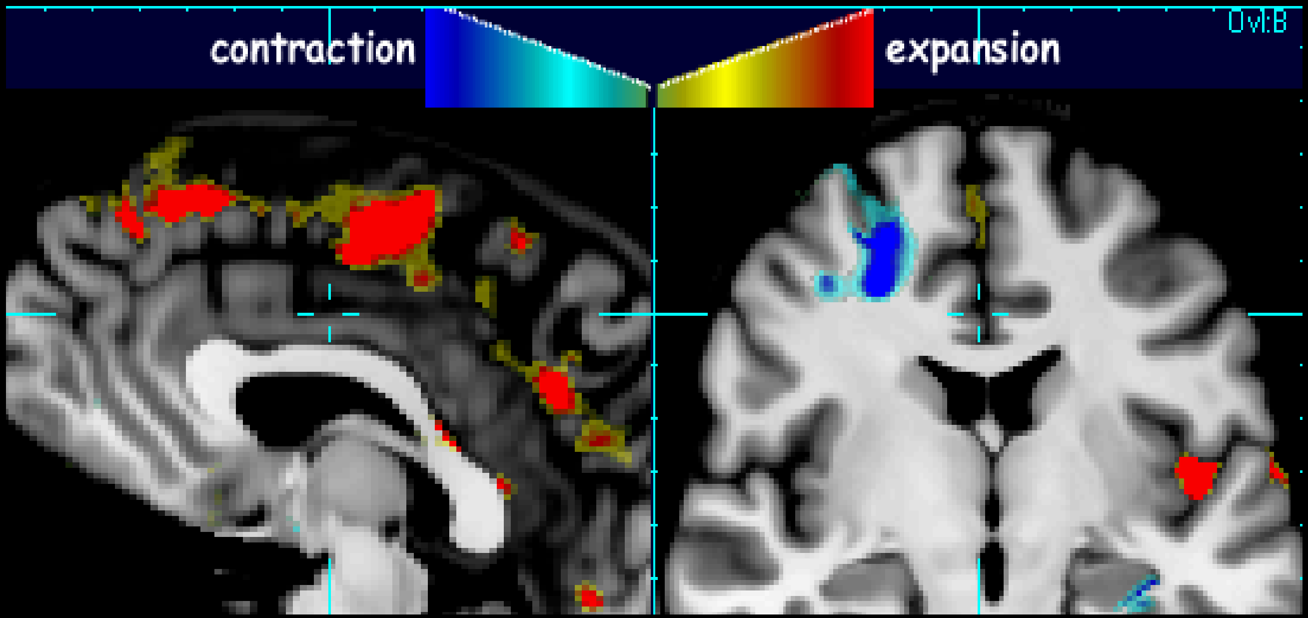
Structure/Function Relationships

WCST

- Wisconsin Card Sorting Test: test of frontal lobe integrity and executive function
- Test a person’s ability to form, maintain, and switch categories (color, number, form)

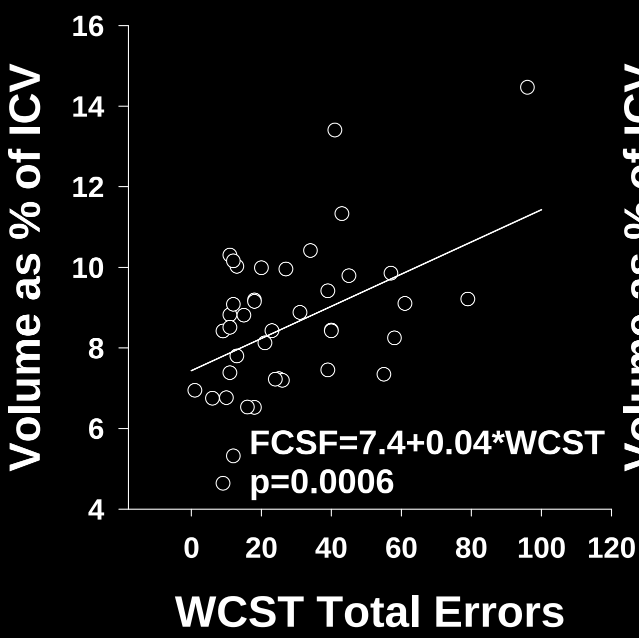


Brain Shape with WCST Scores
t-Statistic Map

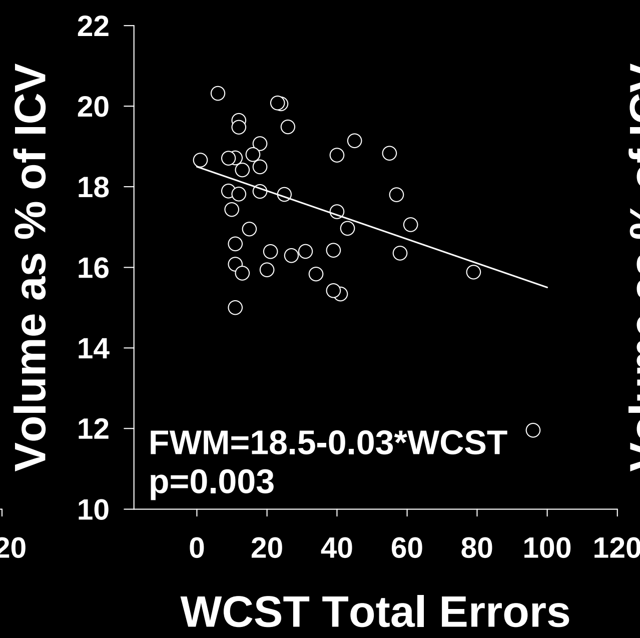


Brain Volume Relationships with WCST Total Errors

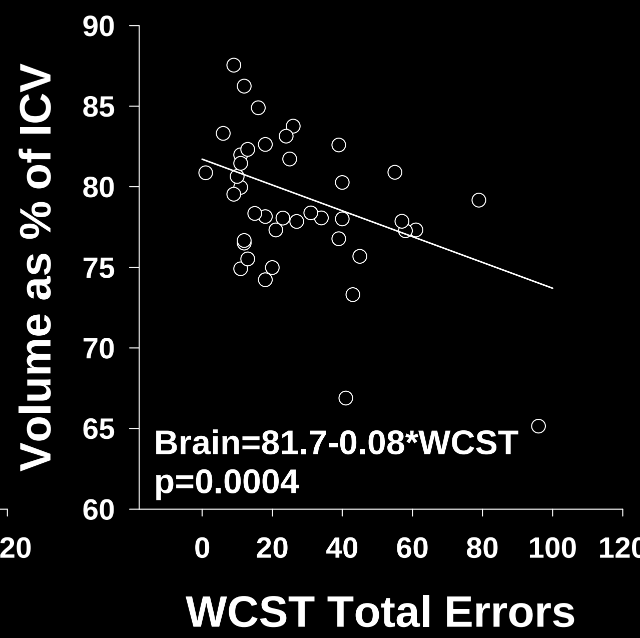
Frontal CSF



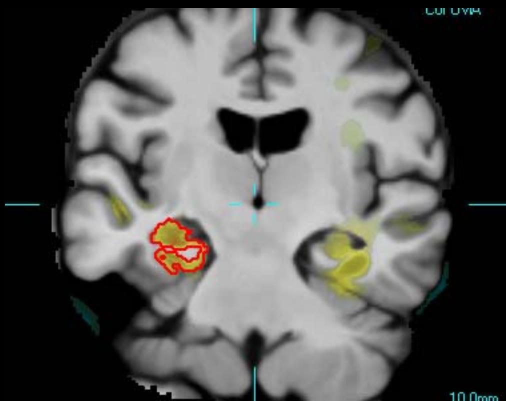
Frontal White



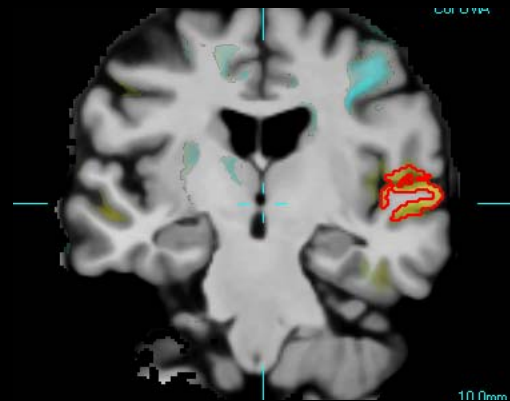
Total Brain



Anatomy Predicting Cognitive Performance

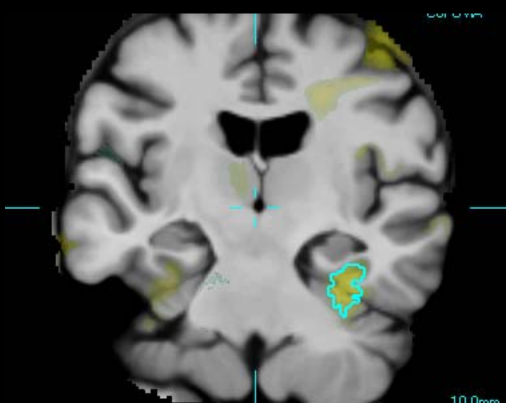


Baseline Memory

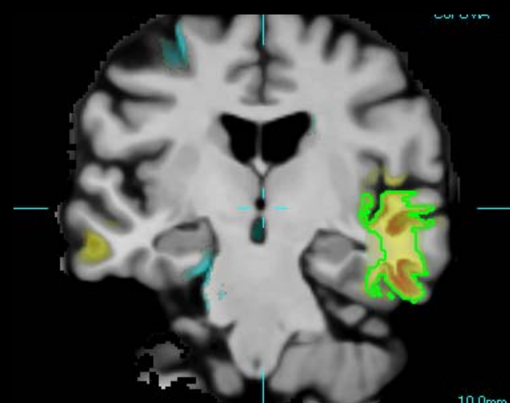


Baseline Object Naming

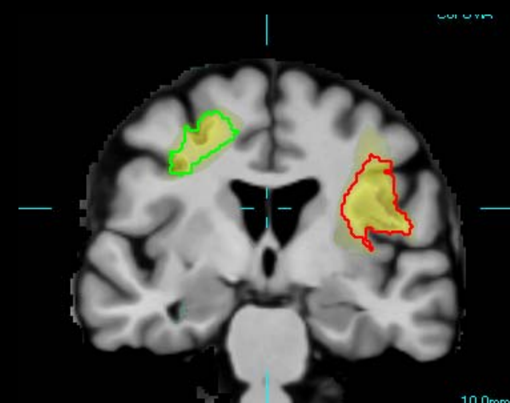
Baseline Executive Function



Memory Decline



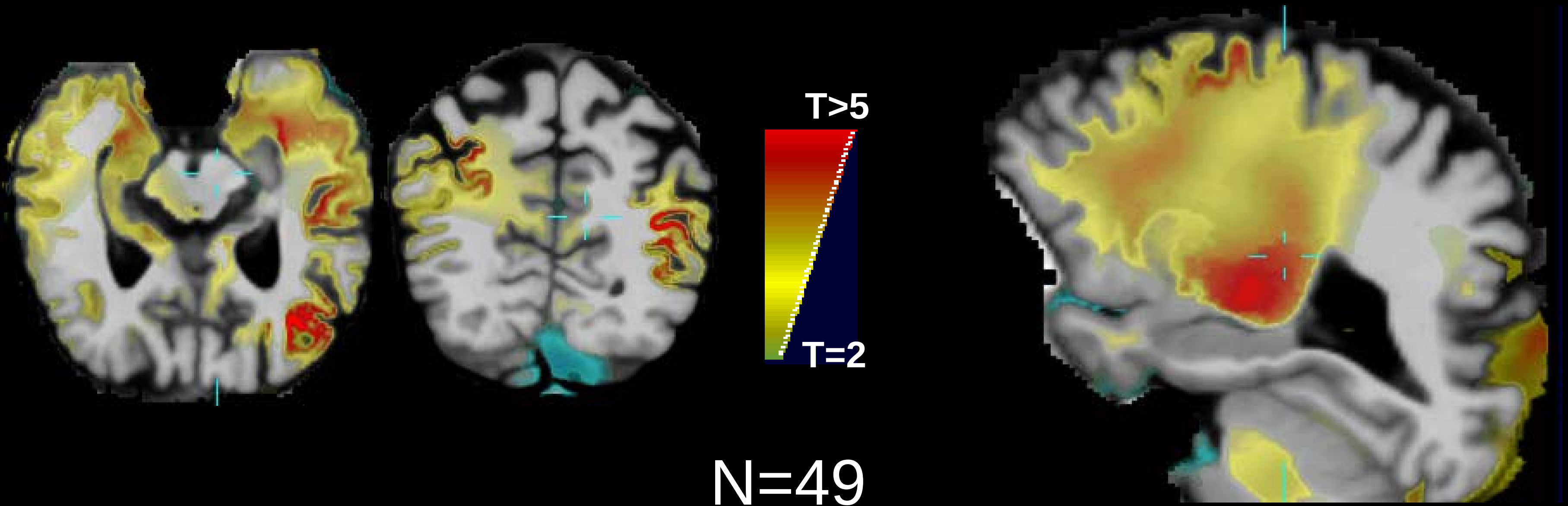
Object Naming Decline



Executive Function Decline

Red/yellow voxels->smaller tissue volume predicts worse cognition or cognitive decline
Blue voxels->greater CSF volume predict worse cognition or cognitive decline

Cognition and Atrophy Rate



N=49

Baseline composite memory scores (covaried for age)

↓ baseline memory scores associated with ↑ tissue loss over time in:

- hippocampus and ERC
- temporal lobe WM and GM
- parietal lobe bilaterally

Baseline composite executive function scores (covaried for age)

↓baseline executive scores associated with ↑ tissue loss over time in:

- frontal WM and GM
- subcortical regions

Co-varying Maps of Atrophy Rate with Maps of Atrophy State

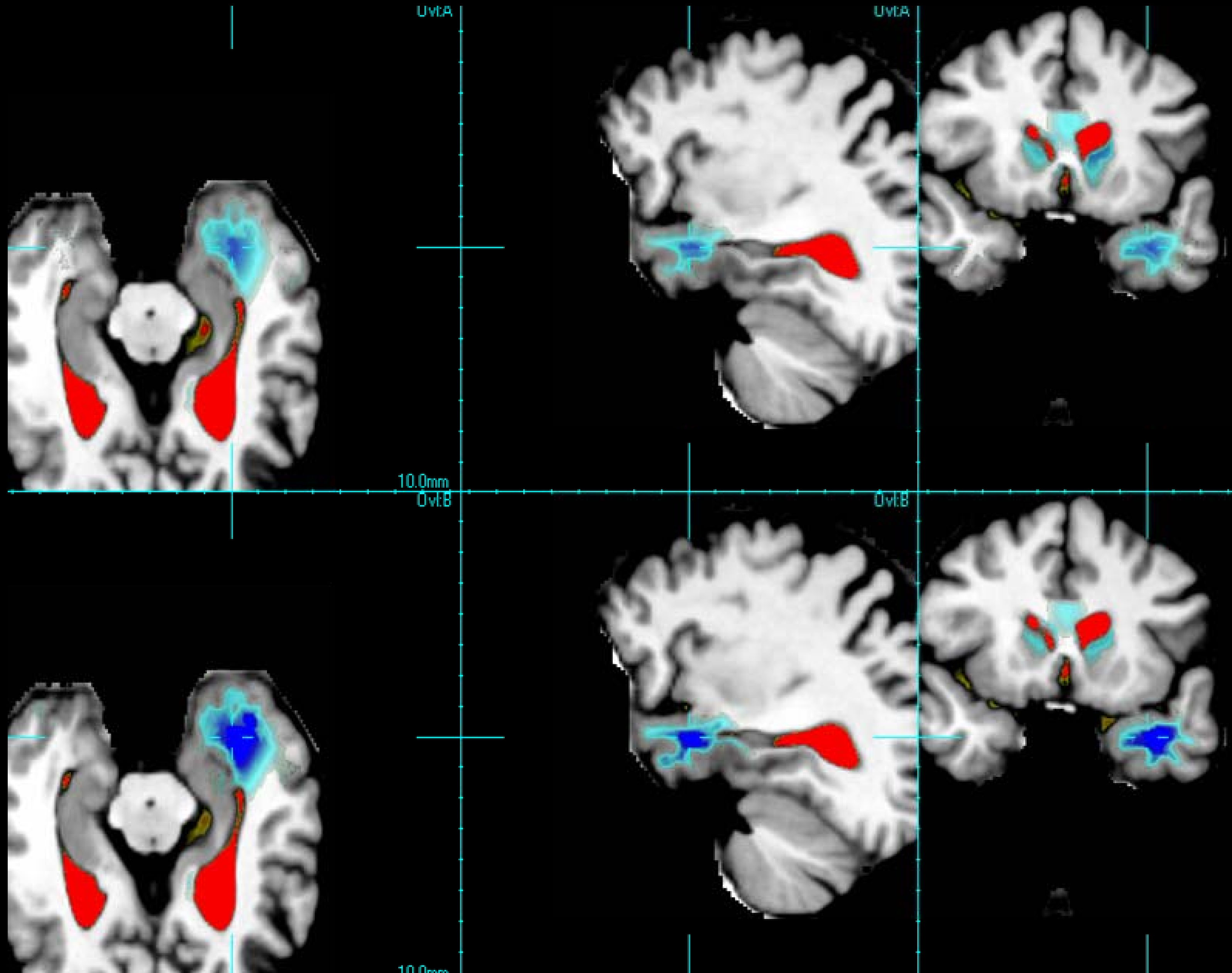
$y(v_i) = A(v_i)\beta(v_i)$

- For parameter estimates:
  - Last column of A **changes** for every voxel
  - solving for x(v) computationally intensive
- For t-statistics
  - diagonal entries of $(A^TA)^{-1}$ must be re-computed for every voxel

Cholesky Decomposition: Advantage with A(v_i) $A^TA=LL^T$

$$\begin{bmatrix} c_1\cdot c_1 & c_1\cdot c_2 & \cdots & c_1\cdot c_p \\ c_1\cdot c_2 & c_2\cdot c_2 & \cdots & c_2\cdot c_p \\ c_1\cdot c_3 & c_2\cdot c_3 & \cdots & c_3\cdot c_p \\ \vdots & \vdots & \ddots & \vdots \\ c_1\cdot c_p & c_2\cdot c_p & \cdots & c_p\cdot c_p \end{bmatrix} = \begin{bmatrix} L_{11} & 0 & 0 & 0 & 0 \\ L_{21} & L_{22} & 0 & 0 & 0 \\ L_{31} & L_{32} & L_{33} & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & 0 \\ L_{p1} & L_{p2} & L_{p3} & \cdots & L_{pp} \end{bmatrix} \begin{bmatrix} L_{11} & L_{21} & L_{31} & \cdots & L_{p1} \\ 0 & L_{22} & L_{32} & \cdots & L_{p2} \\ 0 & 0 & L_{33} & \cdots & L_{p3} \\ 0 & 0 & 0 & \ddots & \vdots \\ 0 & 0 & 0 & 0 & L_{pp} \end{bmatrix}$$

To calculate L_{pj}, need only last row of A^TA and previously computed L_{ij}. Most of L can be computed once, only update last row at each voxel.



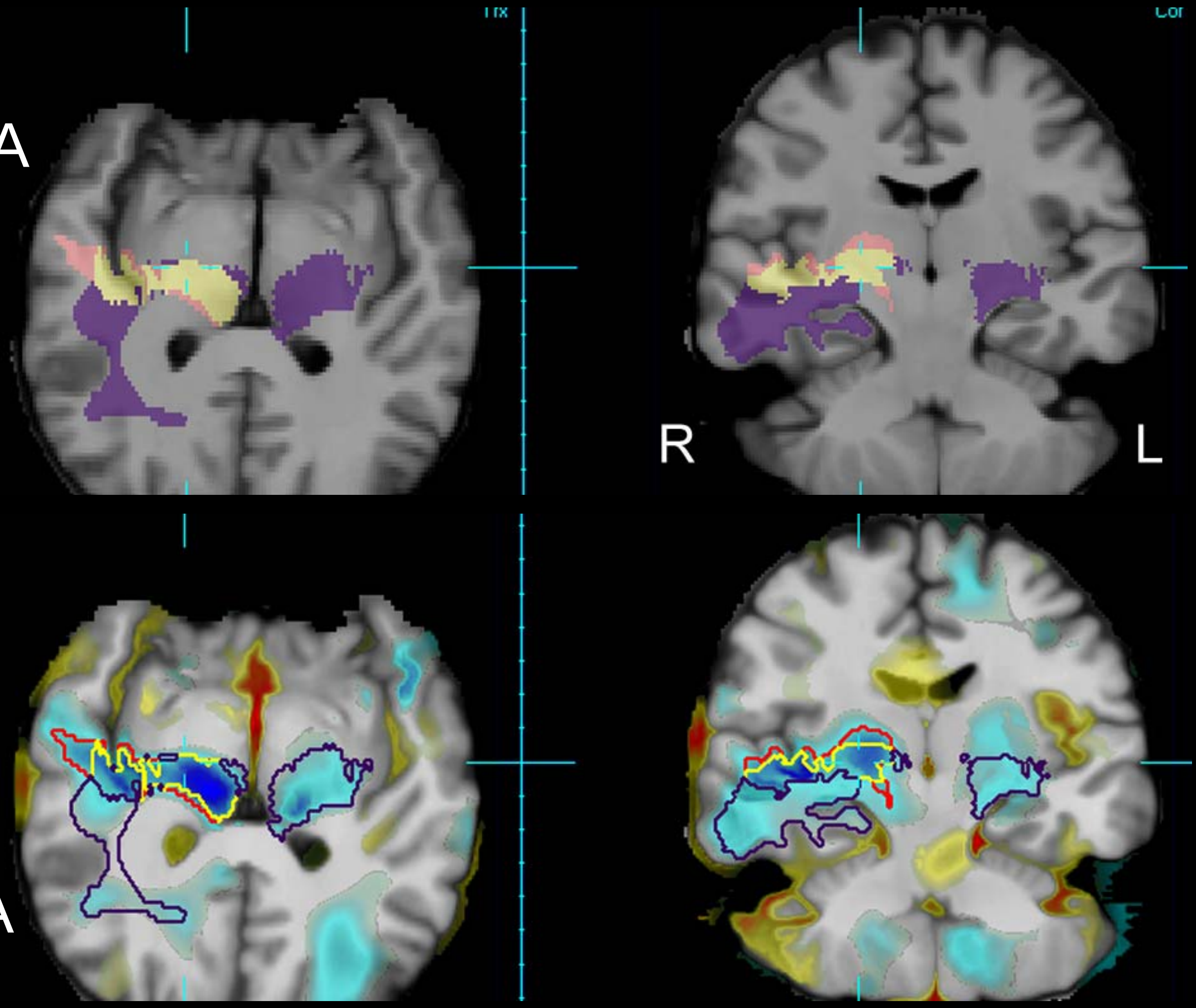
Ovl:A
Ovl:A
10.0mm
Ovl:B
Ovl:B
10.0mm

Common Patterns of Atrophy

- Overlap in brain regions underlying alcohol and tobacco dependence reported
- Does smoking exacerbate alcohol-related atrophy?
- Are there brain regions showing smoking-related atrophy but no alcohol-related atrophy?
- Create t-statistic maps of nsRA vs LD and sRA vs LD, compare t-statistic maps

Smoking Associated with More Widespread Atrophy

Red: nsRA only
Yellow: sRA and nsRA
Purple: sRA only



Tissue reductions:
Red: 11%
Yellow: 11%
Purple: 10% in sRA
5% in nsRA

Summary

- Deformation morphometry is useful for measuring
  - differences between subjects
  - Group differences in within subject longitudinal change
- Can relate anatomy to clinical and functional variables

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